9

Tetanus

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Tetanus is a completely preventable disease caused by contamination of wounds with an anaerobic bacillus, *Clostridium tetani*. The organism is ubiquitous in soil and dust and has the ability to form highly resistant spores. It exists harmlessly in the gut of many animals, including man. If the pathogen is introduced into necrosed tissues, it multiplies and produces a powerful neurotoxin. Tetanus is an endemic environmental hazard, rather than a communicable disease, and consequently does not spread in explosive epidemics (Cvjetanovic, Grab, and Uemura 1978a).

Tetanus in newborns is caused by infection resulting from unsterile methods of cutting the umbilical cord or dressing the stump. The first sign of neonatal tetanus (NNT) is the baby's inability to suck and swallow when a few days old. This inability is due to rigidity of the lips and mouth (lockjaw), which causes a characteristic ironic smile (*risus sardonicus*). Rigidity quickly develops throughout the body, often accompanied by generalized convulsions. Death, usually caused by respiratory failure, occurs between six and ten days of life, two to three days after the onset of symptoms.

In children and adults, tetanus infection follows puncture wounds, cuts, and burns. Cases have been documented that resulted from ear and skin infections, nonsterile injections and surgical procedures, ear-piercing, scarification rituals and tattoos, circumcision, and animal bites or scratches. A relatively common cause of tetanus in adult women is postabortal or postpartum contamination of the uterus, which is associated with a high risk of fatality. Frequently, the portal of entry in non-neonatal tetanus cannot be determined by either the patient or physician.

The World Health Organization (WHO) estimates the case-fatality rate (CFR) of untreated neonatal tetanus to be 85 percent (Stanfield and Galazka 1984; Galazka and Stroh 1986). Marked declines in CFRs in some hospitals are due to control of respiration by medicated relaxation and mechanical ventilation (Simonsen, Bloch, and Heron 1987). Wide variation in CFRs among treated NNT patients has been reported (Bytchenko 1966) and reflects treatment regimens, the vigilance and skill of nursing care, and methods of calculation. In many instances, significant numbers of terminal patients leave the hospital against medical advice and are recorded as surviving patients. In one series of hospital patients, if all those who left against medical advice are assumed to have subsequently died, which is most probable, the CFR increases from 50.6 percent to 92.6 percent (Al-Mukhtar 1987). If only known outcomes are included in the denominator, the CFR in the above study is 87 percent.

Sharma and Sharma (1982) estimate from several hospital studies that the duration of clinical sickness is nineteen days for newborns who recover and three days for those who die. Recovery in younger persons is usually complete.

On the basis of available evidence, the CFR for non-neonatal tetanus (non-NNT) is estimated to be 40 to 50 percent, and the duration of clinical illness in adults is estimated to be 14 days for those who recover and 4.5 days for those who die (Sharma and Sharma 1982). Rey, Diop-Mar, and Robert (1981) estimate the duration of hospital stay to be between 20 and 40 days. As with NNT, the CFR is largely due to treatment regimens, availability of skilled care, and age distribution of infected patients. The prognosis is poorer in the elderly, who represent a large proportion of all tetanus patients in industrial countries. Some authorities report that survivors do not suffer from incapacitating sequelae (Rey, Diop-Mar, and Robert 1981), whereas others report persisting vertebral changes, ophthalmological changes, limb deformity, and the need for convalescent physiotherapy (Sénécal 1970; Veronesi and Focaccia 1981). Older patients are more likely to suffer sequelae because of exacerbation of preexisting conditions. As tetanus does not confer immunity, reinfection is possible. Given the very high incidence and CFR of neonatal and non-neonatal tetanus in developing countries, the most effective strategy is to prevent the disease from occurring in the first place.

Public Health Significance of Tetanus

A sizeable body of literature exists on the public health significance of tetanus in both industrial and developing countries. Despite this, tetanus remains a neglected disease.

Past and Future Trends in Incidence

Well into the twentieth century, NNT continued to cause high mortality in today's industrial countries. A review of the experience in these countries is instructive.

The decline of NNT in industrial countries to the point of virtual elimination began before the widespread introduction of tetanus toxoid (TT) immunization for children or adults in the 1950s (Heath, Zusman, and Sherman 1964; Bytchenko 1972; Christensen 1972a; Simonsen and others 1987). The decline was due to improved socioeconomic conditions (for example, wearing shoes), sanitation and personal hygiene (for example, cleaner maternal deliveries and immediate treatment of wounds), and advances in wound management (for example, passive immunization with antitetanus serum [ATS] derived from horses). Increasing urbanization, decreasing proportion of the population engaged in agriculture, mechanization of agriculture, increasing use of chemical rather than animal fertilizers, and falling fertility were important factors contributing to the decline. Hygiene associated with childbirth improved (for example, hand washing and cord care) and the proportion of deliveries conducted by trained health workers either at home (as in Holland) or in health facilities increased.

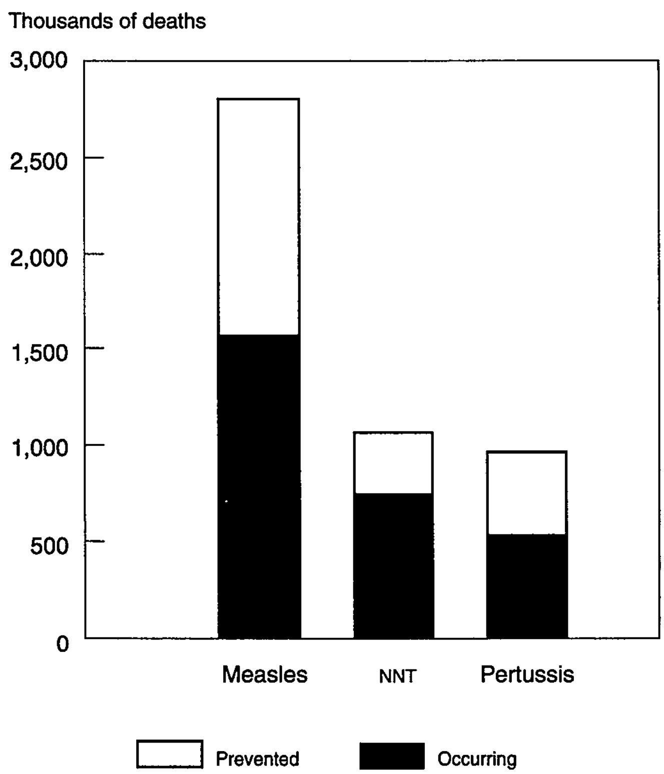
In the United States, NNT incidence declined from 64 per 100,000 live births in 1900 to about 1 per 100,000 live births in the early 1960s (LaForce, Young, and Bennett 1969). In Japan, NNT mortality reached a similar level of 1 per 100,000 live births by 1968, despite a rate of nearly 40 per 100,000 live births only twenty years before. This rapid decline occurred in the absence of a TT immunization program, which was not introduced until the 1970s (Ebisawa 1967, 1972). The control of NNT during the 1970s and 1980s in industrial countries occurred largely because of aseptic obstetric practices. The elimination of NNT owed much to the widespread immunization of children during the 1950s, which led to a cohort of women of childbearing age who could pass maternal antitoxin to their offspring (Christensen 1972a; Simonsen 1989). The fall in non-neonatal tetanus experienced in industrial countries, particularly in children and young adults, was hastened by mass immunization of males and females with TT (Stanfield and Galazka 1984; Simonsen, Bloch, and Heron 1987).

Although instructive, the experience of declining tetanus incidence and improved control in industrial countries is not germane to the situation prevailing in developing countries. With a few notable exceptions, documented levels of NNT today in developing areas are much higher than have ever been reported for today's industrial countries, and few cases are brought to health facilities. In many countries, prospects for rapid improvement in socioeconomic development or in the proportion of births delivered hygienically are not encouraging. Even where birth rates are falling, more babies are being born because of the increased numbers of women of childbearing age. Yet in the second half of this century, TT—an effective and affordable control measure—has become available, along with a structure of national immunization programs through which it can be delivered. Pioneering field trials in developing countries during the past thirty years have demonstrated dramatically that, despite a contaminated environment, NNT can be rapidly controlled and even eliminated by wide use of TT immunization (Schofield, Tucker, and Westbrook 1961; Newell and others 1966; Berggren and Berggren 1971; Black, Huber, and Curlin 1980).

Unless significant resources are allocated to its rapid reduction, tetanus incidence will decline slowly in developing countries. The pace of decline will be a function of epidemiological risk factors, demographic trends, use of health care, socioeconomic change, political will, resource allocations, and technological advances. The most important factors for the reduction of tetanus cases in developing countries will be increased immunization coverage among children and adults with preparations containing tetanus toxoid, urbanization and urban growth, and declining total fertility rates. The possible development of a high-potency single-dose TT will also hasten the prevention of tetanus.

To accelerate this decline in tetanus, the World Health Assembly of WHO in 1989 set a goal for the Expanded Programme on Immunization (EPI) of global elimination of NNT by 1995. The goal itself has generated increased recognition of the public health importance of NNT. The degree of political will engendered and allocation of required resources will de-

Figure 9-1. Measles, Neonatal Tetanus, and Pertussis Deaths Prevented and Occurring



Note: NNT deaths prevented = 325,000; NNT deaths occurring = 754,000.
Source: WHO/EPI 1989b.

termine whether as many as 8 million babies and 2 million children and adults (at current incidence rates) die from tetanus during the 1990s.

Tetanus: A Neglected Disease

With the exception of measles, NNT kills more children than any other vaccine-preventable disease. Called a disease of "peculiar quietness" (Tateno, Suzuki, and Kitamoto 1961), tetanus may be the most underreported lethal infection in the world. If tetanus had the potential to spread in sweeping epidemics or if the disease left lasting disability like polio, or if it occurred primarily in adults like tuberculosis, NNT would probably have attracted the attention of public health authorities long ago.

Instead, NNT kills its victims, who are generally born at home, before they are old enough to be registered or missed by the health system. Routine disease surveillance systems in most developing countries detect only a small fraction of cases, less than 5 percent according to WHO (WHO/EPI 1982). Lacking its own three-digit code in the *International Classification of Diseases* (WHO 1977), NNT is frequently not reported separately from cases of non-NNT, despite epidemiologically significant differences in risk factors and options for prevention. As a result, NNT incidence is often hidden within aggregate figures for "infections specific to the perinatal period" or cannot be disaggregated from tetanus in broader age groupings (for example, from birth to age four).

Neonatal tetanus is there to be found, if one looks for it. A single hospital sometimes admits more patients with NNT than are reported for the entire country (Stanfield and Galazka 1984; Betts 1989). In early global reviews of hospital data, NNT was frequently found to be the leading cause of death in pediatric wards (Bytchenko 1966; Miller 1972). Just as reported smallpox incidence in Ethiopia, India, and elsewhere rose precipitously in the face of stepped-up control and improved surveillance (Fenner and others 1988), so too the number of cases of NNT reported by a hospital in a rural area of Haiti with a successful control program increased even as incidence per 1,000 live births dropped (Berggren 1974a). In an area of Indonesia with a history of regular reporting through designated sentinel surveillance posts, NNT incidence was five times higher than indicated by the routine surveillance network operating in the same area (WHO 1986).

Neonatal tetanus also is neglected for sociocultural reasons. The family of the baby with NNT is typically, but not exclusively, poor and illiterate and does not view the disease as a biomedical entity amenable to modern medical treatment. From widely scattered parts of the world, it has been reported that the supernatural nature of the signs of NNT suggests some sort of spirit possession (Schofield, Tucker, and Westbrook 1961; Chen 1976; Bastien 1988; Blanchet 1989; Pillsbury 1989). In some areas of presumably lower incidence, NNT is not clearly distinguished from a larger syndrome affecting newborns (Bastien 1988; Nichter 1990). Cases of NNT are likely to be concealed in some cultures, where it is perceived as a punishment from God (Solter, Hasibuan, and Yusuf 1986), possibly because of parental wrongdoing (Bastien 1988). Traditional prohibitions often preclude travel by the mother and newborn in the intimate and secluded period immediately after delivery.

Current Magnitude of Tetanus

The magnitude and preventability of tetanus has been highlighted in several important papers in which the researchers attempted to define the public health agenda for the 1980s. In arguing for selective primary health care, Walsh and Warren (1979) consider NNT to be in the highest priority group for disease control because of its high incidence, high mortality, and cost-effective and feasible means of control. In struggling with problems of scarcity and choice, Evans, Hall, and Warford (1981) conclude that the investment policies of donor agencies should redirect resources to the areas of greatest need with a package of maternal and child health services, including TT to pregnant women. Foege and Henderson (1986) argue that on the basis of cost, feasibility, safety, and effectiveness, the highest priority should be given to immunization against tetanus, measles, pertussis and diphtheria, and polio.

Table 9-1. Estimated Worldwide Morbidity and Mortality from Non-neonatal Tetanus, 1980–1984

Countries	*Population*[a] *(millions)*	*Average morbidity (per 100,000)*	*Number of cases (thousands)*	*Mortality*[b] *(per 100,000)*	*Number of deaths (thousands)*
Developing countries					
Asia[c]	1,510	15–30	226–528	6–14	90–211
Africa	490	15–35	73–172	6–14	29–69
America	370	3–8	11–30	1–3	3–11
Total	2,290		310–700		122–291
Industrial countries	1,160	0.15	2	0.6	1
Total[c]	3,550		312–702		123–292

a. Figures for 1982. This column does not total correctly in original citation.

b. According to a mean CFR of 40 percent (25 percent to 40 percent in some urban hospitals, 40 percent to 60 percent elsewhere in developing countries). In industrial countries, the CFR is nearly the same, despite intensive care, because most patients are elderly.

c. Excluding China.

Source: Rey and Tikhomirov 1989.

Table 9-2. Age Distribution of Patients with Non-neonatal Tetanus and Case-Fatality Rate in Bombay and Dakar

	Bombay[a]				Dakar[b]			
	1954–68		1977–79		1960–67		1985–86	
Age (years)	Percent	CFR	Percent	CFR	Percent	CFR	Percent	CFR
1 month–9 years	47.6	(32.8)	36.1	(6.1)	43.3	(24.9)	39.1	(17.6)
10–19	17.1	(33.7)	14.1	(15.6)	25.0	(24.9)	25.4	(22.5)
20–29	15.1	(61.5)	21.3	(23.5)	12.8	(37.7)	12.6	(45.5)
30–39	11.1	(45.9)	11.3	(38.9)	8.1	(39.2)	6.5	(41.2)
40–49	4.8	(46.8)	8.2	(23.1)	4.9	(36.4)	7.0	(37.8)
50–59	2.9	(49.3)	5.6	(66.7)	n.a.	n.a.	5.3	(46.4)
60+	1.3	(53.3)	3.4	(63.6)	5.8	(63.0)	4.0	(71.4)
Total	99.9	(39.1)	100.0	(21.6)	100.0	(30.0)	99.9	(29.1)

n.a. Data not available.
a. 1954–68 data from Patel and Mehta 1975; 1977–79 data from Vakil and Dalal 1975.
b. 1960–67 data from Rey and others 1968; 1985–86 data from Sow 1989.
Source: Rey and Tikhomirov 1989.

The World Health Organization estimates that tetanus kills 754,000 newborns each year and that another 325,000 deaths are being prevented (WHO/EPI 1989b; see figure 9-1.) Neonatal tetanus typically accounts for one-fourth of infant mortality and half of neonatal mortality in unimmunized populations in developing countries (Galazka, Gasse, and Henderson 1989).

From community surveys, some 270,000 NNT deaths are estimated annually in the Southeast Asia region of WHO and another 200,000 in the African region (WHO/EPI 1987a). Some 130,000 NNT deaths were estimated to occur in seven countries in the Eastern Mediterranean region of WHO in 1981, with 111,000 in Pakistan alone (WHO 1982). Ninety thousand NNT deaths were estimated for the American region in 1984 (Stanfield and Galazka 1984). An additional 60,000 cases, including 40,000 in China alone, are estimated to occur annually in the Western Pacific region (F. Gasse, personal communication, July 3, 1990). These calculations are based on surveys, which will be discussed later.

NON-NEONATAL TETANUS. The magnitude of non-NNT is poorly defined and often overlooked in discussions of tetanus prevention. Stanfield and Galazka (1984) assume that 50 percent of all tetanus cases are non-neonatal. Rey and Tikhomirov (1989) estimate that 300,000 to 700,000 cases of non-NNT, with 120,000 to 300,000 deaths, occurred yearly in the 1980s, excluding those in China (table 9-1). Industrial countries account for less than 2 percent of the total number of non-NNT cases and deaths.

Using age distribution data from four studies conducted from the 1950s to the 1980s in Bombay and Dakar, Rey and Tikhomirov (1989) show that 50 to 60 percent of non-NNT cases and a higher proportion of deaths occur among economically productive individuals from ten to fifty-nine years old (table 9-2).

Following widespread immunization of infants and older children with diphtheria-pertussis-tetanus (DPT) and diphtheria-tetanus (DT) vaccines, an epidemiological shift in the incidence of tetanus toward children and young adults can be expected to occur in developing countries, as it did in industrial countries (Rey, Guillaumont, and Majnoni d'Intignano 1979; Stanfield and Galazka 1984; Cottin 1987; Simonsen, Bloch, and Heron 1987). As recently as the 1950s, NNT in the United States accounted for 25 percent of all tetanus deaths (Heath, Zusman, and Sherman 1964). In Denmark, NNT accounted for more than 50 percent of all tetanus deaths, but since 1970 no NNT deaths have been reported (Simonsen, Bloch, and Heron 1987). In Sri Lanka the proportion of all NNT cases was halved after the first three years (1978–81) of the establishment of the Expanded Programme on Immunization (de Silva 1982). Increased incidence of adult tetanus may occur in some developing countries that are experiencing a demographic transition, where high birth rates in the past outpaced immunization coverage.

Although the proportion of cases which occur at economically productive ages in both developing and industrial countries is likely to increase, the total number of cases at economically productive ages will decline in industrial countries despite aging of the population (figure 9-2). Tetanus will increasingly become a disease of the elderly in industrial countries as a function of poor vaccination coverage and vanishing immunity (WHO/EPI 1981a; WHO/EPI 1983b; Rosmini and others 1987; Simonsen, 1989; Sutter and others 1990).

MATERNAL MORTALITY DUE TO TETANUS. An important though little recognized benefit from immunization of females with TT is the prevention of tetanus mortality in adult women. Mortality is prevented during the period of maternal risk (defined as pregnancy or within six weeks of being pregnant) both from postpartum and postabortal tetanus, as well as from wounds sustained at other times. Tetanus is caused by "inexpert attempts to remove a retained placenta" at delivery and by incomplete abortion (Schofield 1986).

Among 49 women fifteen to fifty years of age admitted with tetanus to one urban hospital in South Africa during a 7.5-year period, tetanus was associated with pregnancy in 20 (40 percent) of these women (Bennett 1976). Seventeen (35 percent) of the total cases were postabortal, two were postpartum, and one occurred during pregnancy. In another review, the genital tract was the portal of entry in 19 percent of more than 500 women with tetanus (Adeuja and Osuntokun 1971). In the United States, LaForce, Young, and Bennett (1969) reported that 6 of 507 tetanus cases were associated with abortion (4) or parturition (2). In the state of Rio de Janeiro from 1966 to 1968, postabortal tetanus constituted 7 (4.8 percent) of the 146 cases with known portal of entry (Ecuador: Ministerio de Salud Pública and UNICEF 1987).

Citing seven studies conducted in India and one each in Japan, Singapore, and Viet Nam, all published from 1960 to 1962, Bytchenko (1966) notes that postpartum and postabortal tetanus (3 to 113 cases, median 17) accounted for 3 to 22 percent (median 8.2 percent) of all cases of tetanus, with CFRs ranging from 64 to 72 percent. A review of 981 tetanus patients admitted to one hospital in New Delhi from 1963 to 1965 found that postabortal and postpartum tetanus caused 47 percent (71) of the 150 cases occurring among women of fifteen to fifty years of age, 25 percent of the 280 female non-neonatal cases, and 7 percent of all tetanus cases (Suri 1967).

In two prospective investigations of maternal mortality in a rural Bangladesh population having a vital registration system, Chen and others (1974) found that maternal deaths (defined as occurring during pregnancy or within ninety days of its termination) accounted for 27 to 30 percent of all adult female deaths. Where cause of death was reported, 3 (7.3 percent) of the 41 maternal deaths were due to postpartum tetanus. Thus, 2 percent of all adult female deaths were due solely to postpartum tetanus. Postabortal tetanus deaths and tetanus not related to pregnancy would further increase the percentage of adult female deaths attributable to tetanus. The tetanus-attributable maternal mortality rate was 56 per 100,000 live births.

Rosenfield and Maine (1985) cite a 1979 WHO estimate that 500,000 females in developing countries die annually from complications of pregnancy, abortion attempts, and childbirth. Maine and others (1987) construct a model for a hypothetical population of 1 million with a crude birth rate of 46 per 1,000 and a maternal mortality rate of 800 per 100,000 births, but they assume a low proportion (2 percent) of maternal mortality to be due to tetanus. The tetanus-attributable maternal mortality rate in this case would be 13 per 100,000 live births.

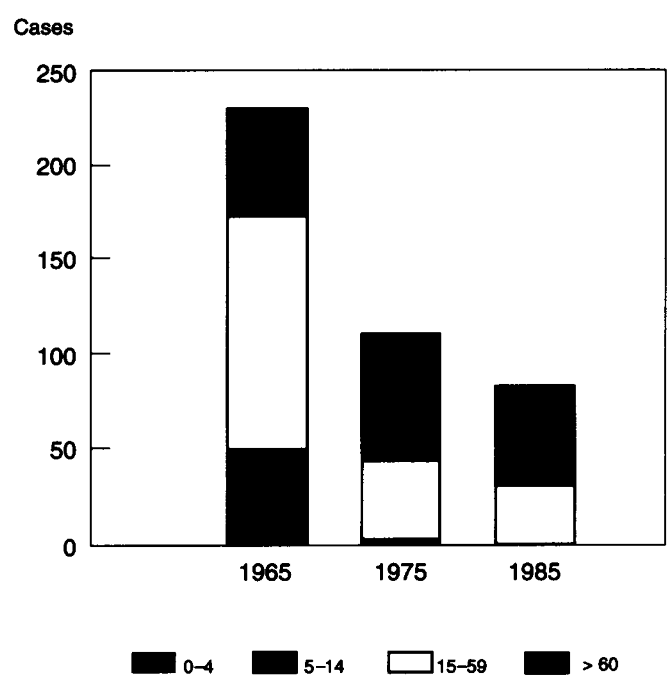
Tetanus represents an important cause of preventable maternal mortality, although it is sometimes only mentioned in passing in references on safe motherhood (Herz and Measham 1987; Royston and Armstrong 1989). A global review of existing data to determine the magnitude of maternal mortality due to tetanus has recently appeared (Fauveau, Mamdani Steinglass and Koblinsky 1993). From 15,000 to 30,000 deaths due to postpartum and postabortal tetanus are estimated to occur annually.

NEONATAL TETANUS. Much more is known about NNT than about non-NNT or maternal tetanus. Retrospective community surveys using a cluster sampling methodology have been conducted widely since the late 1970s to determine mortality from NNT and to elucidate its epidemiological features (Galazka and Stroh 1986). The surveys generally use a short recall period of four to thirteen months and rely upon a "verbal autopsy" method based on the classic symptoms of NNT (ability to suck during first two days of life, followed by cessation of sucking, stiffness, spasms, and death within the first month of life). As of 1989, forty-two countries had conducted more than seventy-five of these surveys (WHO 1982; Gasse 1990; see table 9-3).

Mortality from NNT ranges from as low as 0 to 2 per 1,000 live births (in Tanzania, Congo, Lesotho, Jordon, Tunisia, and Sri Lanka) to 30 to 67 per 1,000 live births (in Pakistan, Bangladesh, and India). Among surveys which detected NNT and reported the proportion of neonatal deaths due to tetanus, 6 percent (in urban areas in West Bengal, India) to 72 percent (in rural areas in Uttar Pradesh, India) of neonatal mortality was attributable to tetanus (WHO 1982).

The surveys have shown that whenever neonatal mortality exceeds 30 per 1,000 live births, tetanus is invariably a substantial contributor (REACH 1989; see figure 9-3). In some developing countries where measles immunization coverage has rapidly increased, NNT could soon overtake measles as the leading cause of mortality among the vaccine-preventable diseases (WHO/EPI 1987a). These surveys have succeeded in alerting many national decisionmakers about the magnitude of NNT as a public health problem. On the basis of the surveys, WHO estimates that only 2 percent and 5 percent of NNT cases have been reported in the Eastern Mediterranean and Southeast Asian regions of WHO, respectively (WHO/EPI 1982).

Figure 9-2. Reported Tetanus Cases in Poland, by Age, 1965, 1975, 1985



Source: Galazka and Kardymowicz 1989b.

Table 9-3. Estimated Neonatal Mortality and Neonatal Tetanus Mortality Rates Based on Special Community Surveys, 1978–1989
(per 1,000 live births)

WHO region	Country	Year	Number of live births surveyed	Mortality rates: Neonatal	Mortality rates: NNT	Percent of neonatal deaths due to tetanus
Africa	The Gambia	1980	4,976	—	11	—
	Cameroon	1982	2,102	—	7	—
	Côte d'Ivoire	1982	2,324	34	18	51
	Malawi	1982	2,081	29	12	41
	Ethiopia	1983	2,010	8	5	53
	Zimbabwe	1983	4,103	10	4	39
	Zaire	1983	4,106	—	9	—
	Senegal	1983–86	4,164	51	16	31
	Cameroon	1984	2,118	—	8	—
	Uganda	1984	525	38	15	40
	Togo	1984	4,966	11	6	52
	Burundi	1984	3,099	—	8	—
	Kenya	1984–85	6,566	16	11	67
	Lesotho	1986	—	—	4	—
	Zambia	1986	3,741	14	4	30
	Tanzania (Zanzibar)	1988	2,269	9	2	25
	Congo	1988	3,524	15	2	15
	Ghana	1989	2,694	26	7	29
	Kenya	1989	2,556	21	3	15
	Lesotho	1989	2,467	4	0	0
	Madagascar					
	Urban	1989	3,133	7	0.1	2
	Rural	1989	2,772	2	0.8	38
	Niger	1989	2,550	26	9	33
	Tanzania					
	Kagera	1989	2,118	—	3	—
	Morogoro	1989	2,129	—	3	—
Eastern Mediterranean	Dem. Yemen	1981	6,224	19	4	20
	Egypt (urban)	1981	—	—	3	—
	Pakistan	1981	13,858	52	31	60
	Somalia	1981	5,781	91	21	23
	Sudan	1981	9,632	29	9	32
	Syrian Arab Republic	1981	6,762	—	5	—
	Yemen Arab Republic	1981	5,191	31	3	8
	Jordan	1983	2,850	7	2	13
	Pakistan	1984	9,925	—	28	—
	Iran, Islamic Rep. of	1985	144,000	21	5	24
	Egypt	1986	8,286	12	7	58
	Pakistan	1987	5,859	14	4	29
	Tunisia	1988	9,478	15	2	9
Southeast Asia	Bangladesh	1978	2,432	48	27	56
	Indonesia	1979	1,570	49	23	46
	Indonesia	1980	3,933	—	12	—
	Nepal	1980	3,346	37	15	39
	Thailand	1980	13,659	21	5	23
	India					
	Rural	1980–81	23,482	19–93	5–67	16–72
	Urban	1980–81	25,843	5–26	0–15	0–59
	Bhutan	1982	952	19	13	67
	Indonesia					
	Rural	1982	4,971	21	11	51
	Urban	1982	2,310	17	7	40
	Nepal	1982	1,997	44	24	55
	Indonesia	1983	4,779	—	17	—

WHO region	Country	Year	Number of live births surveyed	Mortality rates: Neonatal	Mortality rates: NNT	Percent of neonatal deaths due to tetanus
	Indonesia	1984	4,836	—	21	35
Southeast Asia	Indonesia	1984	4,769	—	9	—
(*continued*)	Sri Lanka	1984	2,841	15	1	7
	Burma	1985	6,000	18	6	33
	Bangladesh	1986	2,077	82	41	50
	India	1986	2,386	37	5	14
	Indonesia	1986	4,707	—	3	—
	Nepal	1988	728	19	4	23
Western Pacific	Philippines	1982	8,754	13	6	48
	Viet Nam	1985	8,270	12	2	16
	Lao PDR	1985	4,996	16	4	25
	Viet Nam	1989	9,199	8	3	40

Source: Gasse 1990.

Although the NNT mortality figures are so high, some epidemiologists consider them to be lower than the true rates, as early neonatal deaths are often missed on retrospective surveys (Foster 1984). Mortality rates for NNT are underestimated for other reasons as well. In Côte d'Ivoire, the longer the recall period (for example, more than seven months), the more likely mothers forget or are unwilling to report NNT in relation to other causes of neonatal mortality (Sokal and others 1988).

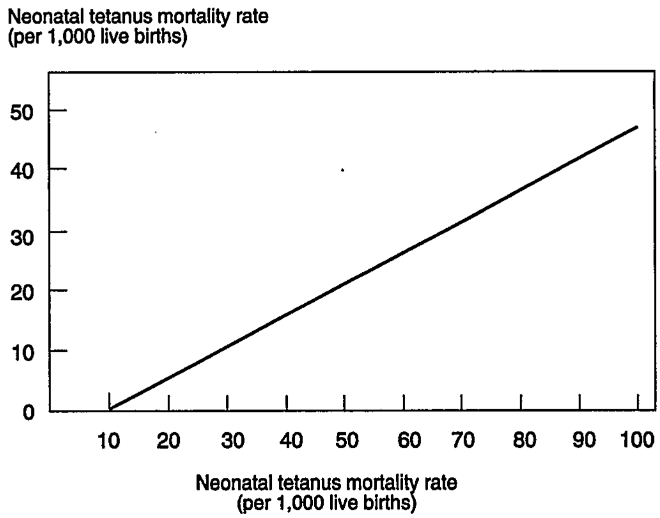
Cultural factors also influence underreporting. For example, female neonatal deaths may be undercounted in some cultures (Galazka and Cook 1985). In Indonesia, Arnold, Soewarso, and Karyadi (1986) found a reluctance to discuss infant deaths. In Senegal, self-reports by families resulted in twenty of twenty-six NNT deaths being ascribed to fevers (one), prematurity or low birth weight (three), other causes (five), and unknown causes (eleven) because of variability in diagnosis through verbal autopsy (Garenne and Fontaine 1986).

Biases also may lead to overestimation of NNT mortality. Gray, Smith, and Barss (1990) question whether the differential diagnoses used in community surveys may lack specificity, so that nontetanus deaths are included in estimations. Furthermore, surveys are conducted in expected high-incidence areas, because the intent is to publicize the magnitude of the NNT problem; generalization of survey results is then likely to overestimate NNT mortality for the country as a whole.

No global review of results of prospective as opposed to retrospective community NNT studies in the same geographical area and time period has been published. In general, very few prospective studies have been conducted, but these too demonstrate the enormity of NNT mortality and approximate the rates found on retrospective surveys. In one of the few community surveys for NNT ever conducted in Latin America, Newell and others (1966) demonstrated that tetanus killed 110 per 1,000 newborns. Like other prospective NNT studies, this double-blind controlled trial relied on registration of all women, establishment and updating of a pregnancy registry during regular home visits by survey staff, and recording of births and deaths. Identifying pregnancies and tracking outcomes eliminates many of the potential biases of the retrospective survey design concerning recall, concealment, and uncertain recording of either live births or deaths.

Longitudinal surveillance by the International Center for Diarrheal Disease Research (ICDDR) in Matlab, Bangladesh, from 1975 to 1977 among a rural population of 260,000 established a NNT mortality rate of 37.4 per 1,000 live births with tetanus responsible for 26 percent of all infant deaths (Chen, Rahman, and Sarder 1980). A prospective survey conducted

Figure 9-3. Total Neonatal Mortality and Neonatal Tetanus Mortality Rates



Note: If the neonatal mortality rate exceeds 30 per 1,000, neonatal tetanus is invariably a substantial contributor.
Source: REACH 1989; data from WHO/EPI 1987a.

by ICDDR in Teknaf, Bangladesh, determined a NNT mortality rate of 27.4 per 1,000 live births with tetanus responsible for 30.8 percent of neonatal and 21.3 percent of infant deaths (Islam and others 1982). These two prospective survey results are within the range reported in the retrospective studies in Bangladesh (table 9-3).

In the Indonesian province of West Java, a prospective study (Budiarso 1984) gave a NNT mortality rate of 14.7 per 1,000 live births, which also falls within the range of retrospective rates already reported. Finally, in a prospective case-control study in a rural area of thirty villages in Senegal, with a total population of 24,000, all births and deaths were systematically recorded for 43 months; the researchers found a NNT mortality rate of 15.9 per 1,000 live births with tetanus accounting for 31 percent of all neonatal deaths (Leroy and Garenne 1991).

This collective body of research has provided important insights into the epidemiological characteristics of NNT. Data are available on seasonality, age at onset of symptoms and death, age and parity of mothers, and circumstances of delivery and cord cutting. The preponderance of male over female deaths has been observed in many, but not all, studies and has been ascribed to real differences in risk of dying; greater likelihood of males being brought to the hospital, where their deaths would be recorded; differences in cord cutting and handling of males and females; and selectivity in recall (Stanfield and Galazka 1984). As analyzed by week-specific mortality ratios by sex, the practice of male circumcision surprisingly does not appear to explain the larger number of male than female NNT deaths.

In cattle- and horse-raising areas of Punjab, Pakistan, NNT mortality was significantly higher than in nearby farming and urban areas, presumably because of a greater risk of exposure (Suleiman 1982). In Uttar Pradesh, India, exposure-related variables (for example, a previous NNT death in the family, presence of large animals in the home, assistance by an untrained birth attendant) were better predictors of NNT than socioeconomic variables, such as education, income, land ownership, and caste (Smucker and others 1980). The significance of epidemiological factors for NNT, as opposed to the role of socioeconomic factors, was noted also in Senegal (Leroy and Garenne 1991).

Surveys in urban areas have shown consistently lower NNT mortality rates than in neighboring rural areas in Egypt, Iran, and India (Galazka and Stroh 1986; WHO/EPI 1987b, 1987c). Nevertheless, urban rates are high in some cities, such as Jakarta, Indonesia, which has a NNT mortality rate of 6.9 per 1,000 live births (Arnold, Soewarso, and Karyadi 1986).

In most studies, NNT was more likely to occur if the child was delivered at home or by an untrained attendant. Hospital delivery, however, does not guarantee protection from NNT, because infection may still occur as a result of unclean delivery or of unhygienic cord dressing after discharge. In Sri Lanka, from 1975 to 1980, nearly half of NNT deaths (206 of 423) and 75 percent of all births occurred in health facilities (de Silva 1982). Nevertheless, the relative risk of NNT in home delivery compared with that in delivery in a health facility was still three to one in Sri Lanka (Foster 1984).

In one Indonesian survey, a NNT mortality rate of 23 per 1,000 live births was recorded for babies whose mothers had no prenatal contact with health facilities, as opposed to only 4 per 1,000 for those whose mothers had at least two contacts (WHO/EPI 1983c). In another study in Indonesia, however, NNT mortality rates were similar regardless of the number of prenatal contacts, because TT was not being systematically given (Solter, Hasibuan, and Yusuf 1986). In a prospective study in Senegal, it was found that washing hands with soap on the part of the birth attendant had a significant effect on the occurrence of NNT (odds ratio 5.19, $p = .0001$) when other factors were held constant (Leroy and Garenne 1991).

Prevention of Tetanus

Tetanus can be prevented by a variety of approaches at a cost which is affordable by most countries.

Prevention Strategies

Tetanus can be prevented by immunization, clean cutting and dressing of the umbilical cord, and hygienic wound management. In this section we will concentrate on prevention of NNT through immunization, because data from developing countries on the effect of interventions designed to ensure aseptic cord care are limited (Ross 1986a, 1986b) and information on associated costs is practically nonexistent. Likewise, data on the effect and cost of wound management are rare in developing countries.

Immunization against tetanus is achieved by vaccinating different target groups with vaccines such as DPT, DT, TT and Td (tetanus-diphtheria with a reduced component of diphtheria antigen)—all of which contain tetanus toxoid. Tetanus toxoid and Td are suitable for adults, whereas DPT vaccine is given to

Table 9-4. TT Immunization Schedule for Women

Dose	*Time to immunize*	*Percent protected*	*Duration of protection*
TT–1	At first contact or as early as possible in pregnancy	Nil	None
TT–2	At least four weeks after TT+1	80	Three years
TT–3	At least six months after TT+2 or during subsequent pregnancy	95	Five years
TT–4	At least one year after TT+3 or during subsequent pregnancy	99	Ten years
TT–5	At least one year after TT+4 or during subsequent pregnancy	99	Throughout childbearing years[a]

a. Original document states "for life."

Source: WHO/EPI *Programme on Immunization*, 1988b.

children less than five years old and preferably during infancy. The DT vaccine is used for young children unable to receive DPT and is mainly administered in schools. The schedule recommended by the World Health Organization requires five doses of TT for protection throughout the childbearing years (WHO/EPI 1988b; see table 9-4.)

Protective levels of antibody in the woman ensure protection for the newborn (as well as for the mother herself), since antibody crosses the placenta from mother to baby. Studies on the immunological response to TT have been reviewed by Rey (1982) and Galazka (1982, 1983). The standard series of three DPT injections given at monthly intervals during infancy counts as the first two of the five TT injections required for protection throughout the childbearing years.

Tetanus toxoid costs about $0.02 per dose in multidose vials, can withstand temperatures of 37°C for at least six weeks (WHO/EPI 1990), has more than 95 percent efficacy when used according to the correct schedule, and is extremely safe. Nevertheless, less than half the babies in developing countries have immunity at birth against NNT.

Reactions to TT are minor and local, usually lasting less than one day. Severe systemic reactions are rare, occurring in 1 per 50,000 to 250,000 injections (Christensen 1972b; White and others 1973). In the German Democratic Republic, severe residual damage was virtually unknown (WHO/EPI 1983a). Tetanus toxoid can be given at any stage of pregnancy without increased risk of abortion or congenital abnormality (Heinonen, Shapiro, and Slone 1977). Contraindications to TT immunization are virtually nonexistent (Rey and Tikhomirov 1989).

Researchers have documented the effect of TT immunization on reducing NNT mortality and lowering overall neonatal mortality in developing countries using a variety of control strategies. Immunization of pregnant women in Sri Lanka and Burma resulted in rapid declines in NNT (Stroh and others 1987; Galazka, Gasse, and Henderson 1989). In Sri Lanka after the introduction of EPI in 1978, NNT dropped from 2.16 to 0.06 per 1,000 live births by 1986. In Burma, a community survey found that the NNT mortality rate (3 per 1,000 live births) in EPI operational areas was only one-third the rate in other areas (Stroh and others 1987). The effect of three interventions in Burma was calculated to determine their proportional contribution to the reduction in neonatal tetanus mortality (Stroh and others 1987; see table 9-5). Hospital delivery, although highly efficacious (85 percent), contributed to only 17 percent of the reduction in NNT mortality because coverage with this intervention was only 14 percent. The programmatic efficacy, which is a product of the efficacy and coverage of the intervention, was slightly higher for deliveries by traditional birth attendants (TBAs) and much higher when two doses of TT immunization were given to the pregnant woman.

Mass immunization of 95 percent of women of childbearing age with one dose of TT from 1978 to 1979 in Maputo, Mozambique, followed by routine immunization of pregnant women, resulted in an eightfold drop in reported NNT cases in one hospital (Cliff 1985; WHO/EPI 1988b; Cutts and others 1990).

In Haiti, mass immunization of the entire population of a rural area eliminated NNT and reduced non-NNT to a negligible level (Berggren 1974a). A two-round mass TT campaign in 1985 in Pidie District, Indonesia, achieved 84 percent immunization coverage of all women of childbearing age with two doses of TT. Pre- and postcampaign NNT mortality surveys indicated an 85 percent reduction in NNT mortality. This reduction was likely due to the mass TT campaign, because neonatal mortality attributable to causes other than tetanus remained unchanged (WHO/EPI 1988a). Despite some disruption to routine programs, the Pidie campaign covered a high proportion of the unimmunized backlog, resulting in a dramatic reduction in NNT mortality.

Immunization was shown to be dramatically effective in reducing NNT in Colombia (Newell and others 1966), New Guinea (Schofield, Tucker, and Westbrook 1961), Bangladesh (Black, Huber, and Curlin 1980; Rahman, Chen Chakraborty, Yunus, Chowdhury, Sarder, Bhatia, and Curlin 1982), and many other countries. In Bangladesh, varying NNT mortality between the fourth and fourteenth days explained most of the difference in neonatal and infant mortality rates between the Maternal and Child Health (MCH) and Family Planning intervention area and the control area in a population of 260,000 (Bhatia 1989).

Mosley (1989) has argued that, unique among vaccines, TT is highly effective because NNT incidence is high and the disease has high fatality among otherwise healthy persons. For that reason, a disease-specific intervention against tetanus is able to have a large demographic effect. Unlike measles or pertussis-related deaths, which come at the end of a cycle of synergistic insults (infection, growth retardation, and reduced resistance), NNT has a discrete cause and a specific intervention—TT. Consequently, the so-called replacement mortality phenomenon probably does not occur in the case of NNT. Henry, Briend, and Fauveau (1990) state that given the con-

Table 9-5. Effect of Three Different Interventions on Mortality from Neonatal Tetanus, Burma, 1985

Characteristics	Intervention: Immunization with two doses of tetanus toxoid	Hospital delivery	Trained birth attendant
Efficacy[a]	0.91	0.85	0.33
Coverage	0.44	0.14	0.51
Efficacy x coverage	0.40	0.12	0.17
Contribution to reduced neonatal mortality (percent)[b]	58	17	25

a. Defined as:

$$\frac{\text{attack rate without intervention} - \text{attack rate with intervention}}{\text{attack rate without intervention}}$$

b. Defined as:

$$\frac{(\text{efficacy } i \times \text{coverage } i) \times 100}{\text{sum of (efficacy } i \times \text{coverage } i)}$$

where i is intervention.

Source: Galazka, Gasse, and Henderson 1989; based on data in Stroh and others 1987.

straints in Bangladesh on implementing the full EPI, TT (along with measles vaccination) is the most cost-effective immunization strategy for child survival.

Active and permanent immunization of the entire population and of successive cohorts will be required first to control tetanus and then, because of continuous environmental risks of contamination, to sustain its elimination as a public health problem. Each individual will require five doses of the current tetanus toxoid preparation at appropriate intervals for full lifetime protection. Rey and Tikhomirov (1989) propose a three-stage approach for tetanus control: universal immunization of infants, children, and women of childbearing age, including pregnant women; extension of immunization to schoolchildren and high-risk, easy-to-reach adults (for example, military recruits), as well as more systematic prophylaxis of wounds; and extension of immunization to all other adults, including such neglected groups as the elderly and immigrants.

The relative emphasis and timing of each of these control stages is a decision best made at national and subnational levels based on disease epidemiology, organization of health service delivery, operational and behavioral considerations, availability of resources, and the tradeoffs between costs and benefits of early and late control. The appropriate choice and degree of implementation of strategies will depend on whether the goal is total elimination of all tetanus, the total elimination of NNT, or the elimination (that is, control) of both as public health problems.

The advantages and disadvantages of using various immunization strategies and target groups can be delineated (WHO/EPI 1986) on the basis of discussions by Rey (1982), Cvjetanovic and others (1972), and Schofield (1986). (See table 9-6.) There is a long window of opportunity during which it is possible to immunize women to prevent NNT. Ideally, women entering their childbearing years already should have received five doses of tetanus toxoid, which can be in the form of properly spaced doses of DPT or DT (in childhood) and TT. The prevailing belief in many countries that two doses of TT are sufficient must be changed (Steinglass 1989). The earlier the protection, the greater the reduction of non-NNT, as well. This is important, given that the highest age-specific incidence of tetanus after the neonatal period in developing countries is among children.

There is no global blueprint for NNT control. Strategies need to be determined locally and may differ from one area to another within the same country. In Kilifi District, Kenya, a NNT mortality survey conducted in 1989 by the Resources for Child Health (REACH) project found low levels of NNT mortality (3 per 1,000 live births) as a result of high TT coverage through well-attended prenatal care services (Bjerregaard, Steinglass, Mutie, Kimani, Mjomba, Orinda 1993). Targeting TT to pregnant women was an appropriate strategy in this district because prenatal care coverage is high, although mothers with one child were significantly less well protected with TT than were multiparous women.

Elsewhere in Kenya, however, where prenatal care services are unavailable or not used, girls need immunization during early school grades before attrition. School enrollment levels of boys and girls are greater than 95 percent in some of the same districts where TT coverage among pregnant women is lowest. Approximately 90 percent of women in Kenya deliver their babies at home, despite high levels of prenatal care, so a strategy aimed at schoolchildren will help solve the problem of NNT in the medium term while having a marked, immediate effect on non-NNT.

Through high coverage with DPT in infancy and DT in school, some of the Gulf States in the Middle East have virtually eliminated NNT—despite a TT coverage rate in pregnant women of less than 20 percent. Most girls attend school and women deliver their babies in hygienic conditions. Consequently, no systematic attempt to immunize all women to eliminate NNT is indicated. In Denmark, a vaccination program consisting of three high-potency DT injections in infancy and a single revaccination five years later resulted in continuous protection to about the age of twenty-five (Simonsen and others 1987).

A strategy which relies exclusively on the identification and immunization of women during pregnancy is unlikely to succeed in many areas for operational and cultural reasons. Use of prenatal services at fixed facilities is low or frequently occurs very late in pregnancy, leaving insufficient time to administer two doses to the previously unimmunized woman. With periodic outreach or mobile strategies, trying to identify only pregnant women is like trying to hit a moving target when the marksman, or health worker, is also on the move. A campaign in Bangladesh in which health workers went door-to-door to identify pregnant women was not very successful, given shyness to declare pregnancy, outright resistance to vaccination during pregnancy, and the health workers' failure to refer the women for vaccination sufficiently early in pregnancy (Rahman, Chen, Chakraborty, Yunus, Faruque, and Chowdhury 1982).

Historically, the exclusive focus on pregnant women as a target group for TT has been well intended but operationally impractical in many developing countries. Administration of TT to individuals in this high-risk group is known to have an immediate effect on protecting the newborn. But unless the health services are well developed and appropriately used, a target group focusing on pregnant women exclusively will have low programmatic efficacy and will not achieve a rapid reduction of NNT or non-NNT. Thus a population-wide strategy is required because susceptibility to tetanus is general.

For this reason, WHO recommends continuous immunization of women of childbearing age, including pregnant women. Every contact with the health services is an opportunity to screen a woman's TT status and provide immunization. This strategy is less immediate in protecting individual births than one that focuses on women already pregnant, but its effect on the population will be more rapid. For this strategy to work, a change in attitude of health workers, particularly curative staff, may be needed. Because this target group is less specifically at risk than women already pregnant, more doses of TT will be needed per NNT case

Table 9-6. Advantages and Disadvantages of Different Immunization Strategies in the Prevention of Neonatal Tetanus

Approach	*Advantages*	*Disadvantages*	*When to use*
Immunization of pregnant women attending antenatal services	Few additional resources needed Potentially rapid impact on disease incidence	Hesitation about injections during pregnancy Women at highest risk rarely come for antenatal care Only very short periods to immunize women and to maintain immune status	When over 80 percent of pregnant women attend at least twice in antenatal period As part of overall effort to immunize women
Immunization of women of child-bearing age through regular health services	Any contact of women with health worker can be used Better chance of reaching high-risk women (who may not come for preventive care, but would come for curative care for their child)	Cooperation of health staff needed More complex logistics Accessibility of health services may be limited	Preferred when coverage for antenatal care is less than complete and there is reasonable degree of access to general health services May need to be supplemented with (limited) mass campaigns
Immunization of women coming with children to immunization session	Few additional resources needed Women with children are likely to become pregnant again	Women are not reached for first pregnancy Coverage cannot exceed maximum coverage of children	Should be part of any approach If used as only approach, needs periodic supplementation with mass campaigns
Immunization of women coming with or without children to immunization session	Few additional resources needed Women reached for first pregnancy	Accessibility may be limited	Should be part of any approach and may eliminate need for mass campaign if coverage is high
Special outreach clinics (markets, meetings)	Increases accessibility considerably	Needs organization and some extra resources	In places with regular, well-attended markets or other special events and limited access to regular health services
Immunization of schoolchildren	Few additional resources needed Can be incorporated into ongoing school health programs School immunization programs may provide good stimulus for improving health education on immunization	Impact on disease incidence delayed (ten to twenty years) High-risk groups have low school attendance No school health program in most rural areas	Wherever a school health program can be activated without distracting resources from MCH care
Mass campaign	Rapid impact High visibility has good promotional value Men as well as women can be included	Resource intensive Might distract resources from development of regular MCH care May need repetition	Wherever incidence is 10 per 1,000 live births or more When special high-risk areas or groups are not reached otherwise As part of any accelerated immunization activity

Source: WHO/EPI 1986.

averted because many doses will be given to older, less fertile age groups. The World Health Organization recommends the use of long-lasting cards for appropriate screening, immunization, and documentation of protection.

A promising strategy being introduced by the Pan-American Health Organization in Latin America makes use of existing incidence data from routine reporting systems to identify areas at higher-than-average risk for NNT. This strategy permits health staff to target immunization efforts (Cvjetanovic 1972; de Quadros 1990). Another novel strategy is being tried in Indonesia, where prospective brides are required to show proof of TT immunization for marriage registration (Lanasari and Rosenberg 1989).

Economic and Financial Considerations of Prevention

Tetanus has important economic consequences for the developing world. Mortality rates for neonatal tetanus are generally highest in the poorest countries, which have inadequate preventive services.

For infected babies in the poorer countries, tetanus is almost always fatal. Children and adults not adequately protected by TT immunization experience a continuous risk of tetanus from wounds throughout their productive years. Deaths from tetanus, in 40 percent of adult cases and 85 percent of neonatal cases, affect the productive capacity of the population and represent an economic loss to society. Further, hospital treatment of tetanus is expensive for families and society. In countries with limited public health resources, provision of adequate treatment for tetanus constitutes a high opportunity cost compared with health services for other diseases. Given the high cost and poor outcome of treatment, and the fact that most tetanus patients are never brought to health facilities in the first place, the most cost-effective strategy is to prevent this common disease.

The cost to society of tetanus includes economic loss due to death and disability, the cost of treating individuals, and the cost of preventing disease. Although there is a growing body of empirical and theoretical evidence on the cost of preventing tetanus, little work has been done on the loss of productivity because of the disease. In this section we review and discuss cost-benefit and cost-effectiveness analyses of the prevention of NNT and non-NNT through immunization. Other methods of preventing tetanus—such as training TBAs to provide improved obstetrical care—have not been included in the following cost analyses because there is a near total absence of data on costs and the effect of alternative interventions.

Fifteen studies and four simulation models are reviewed (see appendix tables 9A-1–9A-4). The studies, which include six from Africa, six from Asia, and three from the Latin American and Caribbean region, were conducted by a variety of researchers during a twenty-year period, from 1970 to 1990. Examination of TT costs was not the purpose of eight of the studies. In these instances, available cost and coverage data have been used to estimate the cost-effectiveness of immunization strategies.

COST-EFFECTIVENESS STUDIES. The results from cost-effectiveness studies of immunization against tetanus are difficult to compare because of the variability in methods used to determine program costs and outcomes (see appendix tables 9A-1 and 9A-2). Some researchers use actual cost and incidence data, whereas others rely on estimates based on various assumptions. The methods used to estimate program costs vary in four principal ways: (a) type of costs measured, (b) method of allocating shared resources, (c) time frame of analysis, and (d) the strategy and scale of tetanus control.

Researchers measured either the expenditure for the immunization program (Berggren 1974a; Kielmann and Vohra 1977; Rey, Guillaumont, and Majnoni d'Intignano 1970; UNICEF/Jakarta 1985) or the economic costs (Barnum 1980; WHO/EPI 1981b; Robertson and others 1985; Brenzel 1987; Brenzel and others 1987; Shepard and others 1987; de Champeaux and Martin, 1989; Narcisse 1989; Phonboon and others 1989; Brenzel and others 1990; Berman and others 1991).[1] Rey, Guillaumont, and Majnoni d'Intignano (1979) include only vaccine costs in the cost calculations for Dakar, Senegal. In Deschapelles, Haiti, Berggren (1974a) estimated the value of the time spent by health workers to administer tetanus toxoid vaccine during visits to marketplaces, though he used the total expenditure for the five-year program for the cost-benefit calculation of the program. The costs of the Indonesian campaign in Central Lombok reflected UNICEF expenditure and vaccinators' salaries but did not include costs at the national level or a portion of the routine salaries of health officials (UNICEF/Jakarta 1985). Kielmann and Vohra (1977) predicted the cost in Punjab, India, of importing, storing, and transporting vaccine, as well as managing and administering a hypothetical program.

Among the studies in which economic costs were calculated, the identification and calculation of program costs varied. In several studies the researchers adapted methodologies developed for costing EPI (Brenzel 1987; Brenzel and others 1987; de Champeaux and Martin 1989; Narcisse 1989; Phonboon and others 1989; Brenzel and others 1990; Berman and others 1991). The authors of one study measured the incremental cost of adding different vaccines, like DPT, to EPI in Indonesia on the basis of additional inputs and resources required for each (Barnum, Tarantola, and Setiady 1980). Berman and colleagues (1991) were the only researchers who distinctly evaluated the economic cost of a tetanus immunization campaign. The diversity of underlying assumptions, not always explicit in each study, makes comparing results risky.

Cost-effectiveness studies differed in how shared health resources were allocated to tetanus prevention. For instance, the cost of the tetanus component of EPI was estimated to be 37.5 percent of the total cost in the Gambia (Robertson and others 1985). This proportion was based on the number of contacts for tetanus toxoid (three) compared with total contacts for all doses for full immunization (eight). In many studies, the cost of immunizing women with TT was based on the proportion of annual doses administered to women compared with total annual doses given by EPI (Brenzel 1987; Brenzel and others 1987; Shepard and others 1987; de Champeaux and Martin 1989; Narcisse 1989; Phonboon and others 1989; Brenzel and others 1990).

The time frame used in the cost studies affects the results. Although annual costs of a tetanus control program were calculated in most of the cost-effectiveness studies included in this review, there was no uniform time period across all studies. The researchers in several studies evaluated the cost of an immunization program over a period of several years but did not discount costs to a present value estimate (Berggren 1974a; Barnum, Tarantola, and Setiady 1980). Others measured costs for less than one year, for mass campaigns, for example, which last for a period of months (UNICEF/Jakarta 1985; Narcisse 1989; Berman and others 1991). Further, the point at which a cost-effectiveness study is conducted in the life of an immunization program affects the generalizability of the results. Estimates are likely to be located on different average cost curves at different times during the immunization program, making comparisons of efficiency suspect.

The studies focused on routine immunization of pregnant women, or mass immunization of pregnant women or women of childbearing age. The target population, delivery strategy used, and the scale of the intervention differed. Most studies focused on immunization of women with TT. The required number of doses, and therefore contacts, per woman for full protection was two in most studies, although it ranged from one (Kielmann and Vohra 1977) to three doses (Berggren 1974a; Robertson and others 1985). Pregnant women were the target group in seven of the studies, whereas women of reproductive age were the focus in another seven studies. The cost of vaccinating the entire population with TT was calculated in one study (Rey and others 1979). In another, the researchers examined the cost of the tetanus component of DPT for infants in addition to the cost of TT for women (Barnum, Tarantola, and Setiady 1980).

Mass campaign and routine strategies could be compared in only two studies. In Haiti, the cost-effectiveness of mobile teams, rally posts, and national campaign and fixed centers were evaluated (Narcisse 1989). In Indonesia, a provincial-level campaign was compared with routine services (Berman and others 1991). Berggren (1974a) evaluated the cost of the marketplace strategy in Haiti, as well as that of a comprehensive intervention that included TBA training. Some researchers included the cost of providing routine immunization services to women in a sample of health facilities (WHO/EPI 1981b; Robertson and others 1985; Shepard and others 1987; Berman and others 1991; Brenzel and others 1990). Others examined the total cost of a tetanus control strategy at regional, provincial, or national levels.

Because tetanus incidence is influenced by general social and economic factors, attributing the reduction in incidence exclusively to a specific immunization intervention oversimplifies the situation. In Haiti, the incidence of tetanus declined prior to the onset of the immunization program (Berggren 1974a). The training program for TBAs may have contributed to the eventual decline in cases, although the benefit of training TBAs in Haiti is difficult to measure because training overlapped with provision of ATS at delivery and in treatment of tetanus. In few of the studies was immunization other than TT to women considered. Yet DPT and DT administered in childhood primes the immune system so that even a single future dose of TT before a woman delivers could be protective. None of the researchers, with the exception of Rey, Guillaumont, and Majnoni d'Intignano (1979), addressed the cost of reducing both non-NNT mortality and NNT mortality, and none of them examined the costs or benefits of reaching the target population of school-age children.

The comparability of studies is also limited by variability in methods used to assess outcome. Berman and others (1991) were the only researchers who used NNT mortality data derived from community surveys before and after the intervention. Community survey data on NNT mortality were available before the intervention in Deschapelles, Haiti, although comparison of pre- and postintervention rates had to be based on hospital admissions data (Berggren 1974a). The report on the study done in Central Lombok, Indonesia, had data only from a preintervention community survey (UNICEF/Jakarta 1985). Robertson and others (1985) and Kielmann and Vohra (1977) relied on estimates of NNT mortality from community surveys conducted in notably earlier time periods. In some of the above cases, survey results were used even though they represented a wider or different geographic area within the country.

The assumed duration of protection from TT also differed among studies. Kielmann and Vohra (1977) assumed that a single, high-potency dose of TT gave lifelong immunity, but NNT deaths averted were calculated only for the year of the campaign. For the mass campaign in Pidie, Indonesia, Berman and others (1991) considered the duration of protection from two doses of TT to be four years for women of childbearing age but only one year for women immunized through routine prenatal care. Berggren (1974a) assumed that three doses of TT provided protection for a minimum of five years.

None of the studies considered the cumulative benefits from priming the immune system with previous tetanus doses. Assumptions that benefits from TT immunization begin at the start of a campaign or the beginning of a year for a routine program are made in order to reduce the complexity of assessing the cost and effectiveness of immunization.

We conclude, then, that the total costs of NNT reduction are likely to be underestimated in this sample of cost-effectiveness studies, whereas the benefits are overestimated or underestimated among studies and even within studies because of varying assumptions.

COMPARISON OF STUDIES BY PROGRAM STRATEGY. Most of the studies in appendix tables 9A-1 and 9A-2 provide analyses of the two broad categories of strategies for TT immunization: routine programs and mass campaigns. Routine programs may include fixed-facility services, mobile teams, outreach, and other strategies; but separate data are rarely available regarding the cost and cost-effectiveness of each of these types of strategies. As a result, we considered all routine programs as a group and compared them with campaigns. For both campaigns and routine programs, target groups may include all women of childbearing age, pregnant women, schoolgirls, infants, and males as well as females. In table 9-7 we compare the unit costs and cost-effectiveness of the routine programs and campaigns in the review. Included in the table are the median values and ranges summarized by strategy.

We were able to compare the cost of routine TT immunization programs in eight studies (see table 9-7). Several of the studies included estimates for different districts, regions, or types of facilities, yielding a total of seventeen observations for the cost per TT dose, per TT second dose (TT2), per case prevented, or per death averted; the study done in the Gambia was the only one to include estimates under all four categories. The outcome measure most frequently available was cost per TT2.

As shown in table 9-7, the cost per TT dose found in the eight studies ranged from \$0.40 to \$1.76, with a median of \$1.14 (all costs are given in 1989 U.S. dollars). The cost per TT2 ranged from \$0.66 to \$11.87, with a median of \$3.38. The wide range in cost per TT2 may reflect different methods for estimating costs as well as varying levels of efficiency and effectiveness of the programs studied. In only two studies, in the Gambia and Indonesia (Aceh), was the cost per case prevented and the cost

Table 9-7. Unit Costs and Cost-Effectiveness of Tetanus Immunization Programs
(1989 U.S. dollars)

Source	*Location*	*Subdivision*	*Cost per TT dose*	*Cost per TT2*	*Cost per case prevented*	*Cost per death averted*
Routine Programs						
de Champeaux and Martin 1989	Burkino Faso	Yako	1.01	4.15	—	—
		Gourcy	0.64	2.13	—	—
Shepard and others 1987	Ecuador	n.a.	0.40	—	—	—
Robertson and others 1985	The Gambia	n.a.	1.58	5.23	205	228
Narcisse 1989	Haiti	Fixed centers	0.91	—	—	—
		Horse teams	1.14	—	—	—
WHO/EPI 1981b	Indonesia (Central Java)	n.a.	1.18	3.92	—	—
Berman and others 1991	Indonesia (Aceh)[a]	Tanah Pasir	—	2.20	89	105
		Samudera	—	2.76	113	133
		Matangkuli	—	1.47	60	70
		Jeumpa	—	0.66	27	32
Brenzel and others 1990	Sudan	Darfur	1.76	4.80	—	—
		Kordofan	0.86	2.16	—	—
		Capital	1.33	2.84	—	—
		Nationwide	1.73	4.20	—	—
Phonboon and others 1989	Thailand	Hospitals	—	10.25	—	—
		Health centers	—	11.87	—	—
Minimum	n.a.	n.a.	0.40	0.66	27	32
Maximum	n.a.	n.a.	1.76	11.87	205	228
Median	n.a.	n.a.	1.14	3.38	89	105
Campaigns						
Brenzel 1987	Cameroon	n.a.	1.34	4.16	—	—
Berggren 1974[a,b]	Haiti (Deschapelles)	n.a.	0.34	1.05[b]	98[b,c]	115[b,c]
Narcisse, 1989	Haiti	Mass campaign	1.71	—	—	—
		Rally posts	0.21	—	—	—
Kielmann and Vohra 1977	India	Initial	0.29	—	—	97
	(Narangwa)[d]	Maintenance	n.a.	—	—	0.34
UNICEF 1985	Indonesia (Central Lombok)	n.a.	0.23	0.46	44[e]	52[e]
WHO/EPI 1988a	Indonesia	n.a.	0.82	1.84	122	144
Berman and others 1991	(Pidie)					
Rey, Guillaumont and Majnoni d'Intignano 1979	Senegal (Dakar)	Mass campaign	—	—	825[f]	2,750[f]
Brenzel and others 1987	Senegal	n.a.	0.76	—	—	—
Minimum	n.a.	n.a.	0.21	0.46	44	52[g]
Maximum	n.a.	n.a.	1.71	4.16	825	2,750
Median	n.a.	n.a.	0.55	1.45	110	115
Total (routine programs and campaigns)						
Minimum	n.a.	n.a.	0.21	0.46	27	32[g]
Maximum	n.a.	n.a.	1.76	11.87	825	2,750[g]
Median	n.a.	n.a.	0.91	2.80	98	110[g]

— Data not available.
n.a. Not applicable.
a. Protective effect of TT2 on all deliveries within three years not considered; hypothetical incidence data.
b. Derived from information reported in cited document. Schedule included three doses of TT.
c. Excludes an additional 630 non-NNT cases prevented.
d. Study was for one high-potency dose of TT with assumed 80 percent efficacy and lifelong immunity; cost data are hypothetical.
e. Assumed NNT mortality rate equals 28.0 (level for seven clusters in Central Lombok district in a thirty-cluster survey).
f. Includes cost per NNT and non-NNT case and death prevented.
g. Excludes India/Narangwal maintenance level estimate.
Source: See first column of this table and tables 9A-2 and 9A-4.

per death averted estimated.[2] The median cost per case prevented was $89, with a range from $27 to $205. The cost per death averted ranged from $32 to $228, whereas the median was $105. The cost per death averted does not differ greatly from the cost per case prevented because of the high case-fatality rate of neonatal tetanus.

Eight studies listed in table 9-7 also included unit costs and cost-effectiveness for TT programs employing campaign strategies. All but one included estimates of the cost per TT dose delivered. As shown in table 9-7, these estimates ranged from $0.21 to $1.71, with a median of $0.55. One of the lowest estimates ($0.29) was from Kielmann and Vohra's study in Narangwal, India, where a single dose of high-titer (30 Lf per milliliter) calcium phosphate-adsorbed vaccine was used. Kielmann and Vohra (1977) found that this single dose was more effective than three doses of aluminum phosphate-adsorbed TT (10 LF per milliliter) given at one-month intervals. If this assertion is true, it may be more appropriate to compare this cost ($0.29) with the cost per TT2 found in Cameroon ($4.16), Deschapelles in Haiti ($1.05), and Central Lombok ($0.46) and Pidie ($1.84) in Indonesia, because these costs represent the nearest estimates of the cost to protect a woman fully against tetanus for several years. The median cost per TT2 was $1.45.

Estimates of the cost per NNT case prevented are available for four studies, and range from $44 to $825, with a median of $110. The wide range in these estimates may be due in large part to different methods of estimating costs and morbidity reductions.

The median cost per NNT death averted in the studies which examined campaign strategies was $115, reflecting a range from $52 to $2,750. The study in Narangwal, India, includes two estimates for the cost per death averted: one for the initial phase, during which 87 percent of all women from fifteen to forty-four years of age were immunized; the other, a much lower estimate ($0.34), for maintenance of the program, in which only the girls fifteen years of age who enter the eligible cohort each year were immunized. This lower estimate has been left out of the calculation of the median cost per death averted ($115) because of its extremely low and hypothetical nature. Because Kielmann and Vohra (1977) assume lifelong immunity from one dose of high-titer vaccine, they claim that only those women who are entering childbearing age will need to be vaccinated during the maintenance phase of the program. Nevertheless, despite the assertion of lifelong immunity, they include in their cost-effectiveness calculations only those deaths prevented in a single year. This results in an underestimate of the cost-effectiveness, if indeed one agrees with the assumption of lifelong protection.

The extremely high estimate of cost per death averted (NNT plus non-NNT) found in Dakar, Senegal, may have resulted from the high-intensity program used in that instance: seven semestral mass vaccination campaigns were undertaken against tetanus (Rey, Guillaumont, and Majnoni d'Intignano 1979). Moreover, the case-fatality rate was only approximately 30 percent because of the high number of cases in those older than one year, resulting in a large difference between the cost per case prevented and the cost per death averted.

Berggren (1974a, 1974b) estimated that in Haiti an additional 630 cases of non-NNT were prevented. This estimate has not been incorporated into the cost per case or death averted in appendix table 9A-2 or in table 9-7.

In general, this review shows a relatively small range in unit costs and cost-effectiveness. This is surprising given the different methods used in the 15 studies for analyzing the cost and effect of diverse interventions. Little disparity was found between the median values for routine strategies as opposed to campaign strategies, which implies that each strategy may be cost-effective in different circumstances. Whereas median costs per TT and TT2 doses are lower in campaigns, routine strategies were more cost-effective in cases and deaths averted. The choice of strategy must take into account its likely programmatic efficacy—that is, the efficacy of the technology and its expected coverage within the population. In other words, it makes little sense to base a delivery strategy solely on pregnant women attending fixed facilities for prenatal check-ups when, in many countries, only a small minority of women seek prenatal care.

SIMULATION MODELS. We review four hypothetical models which were used to simulate the costs and benefits of alternative tetanus immunization strategies (Cvjetanovic and others 1972; Kessel 1984; Sharma and Sharma, 1984a, 1984b; and Smucker, Swint, and Simmons 1984; see appendix tables 9A-3 and 9A-4). Given the complicated immunologic aspects of tetanus immunization, modeling exercises provide valuable insights from an epidemiologic perspective into the effectiveness of alternative strategies. The greatest weakness of each model is the lack of empirical basis for cost estimates. Kessel (1984) uses an arbitrary system of financial units (from 1 to 100), which ranks the difficulty of implementing alternative immunization strategies with regard to their effect on unit cost per dose (unit costs are expected to rise as the most remote population groups are reached, usually through outreach and mobile services). The results of Kessel's simulations, however, are heavily influenced by the order of magnitude and ranking of these delivery strategies. Cvjetanovic and others (1972) do not consider economic costs of implementing an immunization program but include only vaccine and treatment costs in their model. Sharma and Sharma (1984a, 1984b) base their model on vaccine costs as well, including (unlike the other models) costs of three DPT and three DT shots to young children and schoolchildren, respectively. Only Smucker, Swint, and Simmons (1984) estimate the economic cost of an immunization strategy aimed at TT vaccination of women. Yet they do not consider the integration of TT vaccination (through MCH services) with EPI in India. Joint implementation of immunization of women and children would substantially alter their assumptions about frequency of contact by women with the health system and productivity of health workers (for example, the number of women who could be immunized per day).

Cvjetanovic and colleagues (1972) assume high immunization coverage (90 percent) of pregnant women through routine services and medium coverage (50 percent) of the total population through mass strategies. Empirically, however, these assumptions are reversed. Mass campaigns in Central Lombok and Pidie District, Indonesia; Narangwal, India; and Deschapelles, Haiti, resulted in greater than 80 percent coverage, whereas coverage from routine fixed-facility services was less than 50 percent of the target population of pregnant women. The cost-effectiveness of TT immunization in Kessel's (1984) model is not dependent on coverage levels, which appears counterintuitive from economic theory: average costs change as coverage increases. There is no simulation in any model of the costs and benefits of continuous immunization of women of childbearing age, the strategy recommended by WHO.

As in the empirical studies, varying assumptions were made in the hypothetical models regarding the efficacy of tetanus immunization. The duration of immunity differed among these models from five years (Sharma and Sharma 1984a, 1984b; Smucker, Swint, and Simmons 1984) to ten years (Cvjetanovic and others 1972). The primary series of TT for full protection ranged from two doses (Smucker, Swint, and Simmons 1984 and Sharma and Sharma, 1984a, 1984b) to three doses (Cvjetanovic and others 1972). Sharma and Sharma (1984a, 1984b) include the costs and benefits of three doses of DPT and two doses of DT, whereas Kessel (1984) includes four doses of DPT for preschool children. Cvjetanovic and others (1972) and Sharma and Sharma (1984a, 1984b) include the effect on NNT and non-NNT. Only one model discounts the future costs of the immunization program—at a rate of 12 percent per year (Smucker, Swint, and Simmons 1984). The benefits of the program (for example, deaths averted) are not discounted. Kessel (1984) estimates the effectiveness of tetanus immunization programs by calculating the residual protected fertility achieved by directing efforts at preschool girls, school-age girls, and adult women seeking prenatal care.

As with cost-effectiveness studies, the modeling exercises probably underestimate the costs of delivering immunization services to women and children, whereas benefits are sometimes underestimated and sometimes overestimated. Costs of complementary programs, such as immunization of schoolchildren with DT and infants with DPT and training of traditional birth attendants, are not factored into all the simulations. Similarly, the benefits from NNT reduction are assumed to accrue solely from TT immunization, without regard for active-passive immunization for wound management (including ATS for newborns) and safe deliveries. Thus, the cost per dose and cost per death averted are also underestimated, although, compared with other interventions described in this collection, efforts to control NNT by immunization are likely to be highly cost-effective.

COMPARISON OF RESULTS OF SIMULATION MODELS. Only two of the four models produced usable cost-effectiveness estimates for our present purposes. Although the results of these simulations are not directly comparable to those of the studies, they provide useful insights into the effect of programmatic changes on both the costs and outcomes of tetanus control programs.

Cvjetanovic and others (1972) estimate a range of costs per case prevented from \$245 to \$595 (all costs are in 1989 U.S. dollars), depending on delivery strategy and target population assumed. Smucker, Swint, and Simmons (1984) vary their coverage assumptions and cost estimates to compare a routine program with a campaign using teams of vaccinators. For the campaign approach, costs per TT dose range from \$1.34 to \$2.33, whereas the cost per TT2 varies from \$2.74 to \$5.25. The cost per death averted for this strategy ranges from a low of \$6.75 to a high of \$11.86. The routine program shows somewhat better results: the cost per TT dose ranges from \$0.50 to \$0.98; costs per TT2, from \$1.03 to \$2.20; and the cost per death averted, from \$2.59 to \$4.87. It should be noted that these costs per death averted are far less than the estimates found in all the empirical studies, which may indicate that the cost estimates were too low or that effectiveness assumptions were overly optimistic.

Kessel (1984), using theoretical financial units as a means of comparing the resource requirements of different strategies, concludes that school-based programs are the most economical in the long run because all the residual fertility of the girls is protected. Sharma and Sharma (1984a, 1984b) favor continuous immunization of pregnant women, because mass immunization programs are projected to lead to only short-term declines in tetanus incidence.

REVIEW OF STUDIES AND SIMULATION MODELS: CONCLUSIONS. This review of empirical work and simulation models has shown that immunization of women with TT is a cost-effective means of controlling NNT. The median cost per NNT case averted is \$98 and the median cost per NNT death averted is \$110. These estimates are similar for both routine delivery of TT and campaigns. Although cost-effectiveness is but one criterion for choosing among alternative health interventions, these figures compare favorably with those of other interventions presented in the rest of this collection.

For three reasons, however, the results of this review can be generalized only in a limited fashion. First and most important, the cost of controlling tetanus depends on country-specific characteristics, such as the health infrastructure, delivery strategies used, incidence rates of the disease and coverage rates achieved, and the degree of integration of tetanus control within routine EPI, MCH, and school health services. A country with a well-developed health system and universal access to services is more likely to have lower average costs for a TT immunization program than a country which is still extending basic health services to its population. Integration of tetanus control with basic health services will also tend to reduce average costs.

The empirical studies included in this review reflect the cost of providing services at particular coverage levels through specific strategies. The cost of providing routine services at low coverage levels will not be representative of average costs at higher levels, because economic theory predicts that average costs change as volume increases. All the studies were conducted in countries with high NNT incidence, so results cannot be generalized to countries where tetanus incidence is low, and marginal costs of averting cases will consequently be much higher. In no study or simulation did researchers examine the costs and benefits associated with the continuous immunization of women of childbearing age, the current strategy recommended by WHO for the worldwide elimination of tetanus.

The second reason generalization from country-specific results is difficult is because the opportunity cost of health resources is not consistent among countries. A cost per death averted of $144 in Indonesia (Berman and others 1991) may not represent a different set of tradeoffs for resource allocation from a cost of $228 in the Gambia (Robertson and others 1985), and the situation in Indonesia may differ greatly from that in Haiti ($115 per death averted; Berggren 1974a, 1974b). The decision to invest public resources in tetanus control through immunization must be made within the context of the marginal product resulting from competing country-specific use of those same resources.

Finally, variations in the methods used in the empirical studies and simulations hamper casual generalizations of these results. Still, the convergence of many study results around a figure of $110 per death averted suggests that this median estimate can be used as a starting point for determining resource allocations for tetanus control (see table 9-7). Tetanus control through immunization is a highly cost-effective and inexpensive means of reducing infant mortality in the developing world.

ADDITIONAL ECONOMIC ISSUES. In addition to immunization of women and children, other strategies exist which can potentially affect the incidence of NNT. Among these are training of TBAs in more hygienic delivery practices. Several studies allude to the effectiveness of TBA training in reducing NNT, though controlled community studies with pre- and post-intervention evaluation have been rare (Berggren 1974a; Allman 1986). Allman (1986) estimated TBA training to cost $10 per worker between 1977 and 1982. James Heiby reports a figure of $92.50 per worker in Nicaragua during the late 1970s (cited in Allman 1986).

By contrast, many observers conclude that TBA training is not as effective in preventing NNT as vaccination of women (Ross, 1986a, 1986b; Solter, Hasibuan, and Yusuf 1986; Bhatia 1989; Jordan 1989). The expense of training, supervising, and supporting workers to cover the population would also be prohibitive for most developing countries, particularly if case loads per birth attendant are low. Although some evidence suggests that TBA training programs are relatively effective in reducing nontetanus neonatal mortality (Rahman 1982), large-scale efforts are unlikely to be as cost-effective as targeted immunization strategies for NNT reduction.

Immunization of schoolchildren either with a primary series of DT or with additional reinforcing doses of DT after three doses of DPT has been an underused strategy. Besides a simulation exercise (Kessel 1984) which evaluates the costs and benefits of school immunization against tetanus, little empirical data are available about the potential costs (in relation to benefits) of a nationwide school program in a developing country.

The Kessel (1984) model predicts that school immunization is the most cost-effective strategy for reducing NNT deaths, compared with a preschool program, prenatal clinic, and outreach immunization of pregnant women. This model, however, assumes universal access to education and a well-developed institutional base from which to deliver immunizations. The actual situation in most developing countries differs from these assumptions: access is often not universal and attrition rates are high, particularly among young girls—the target population for immunization. Similar to the health sector, the education sector is weak institutionally and financially in most developing countries. Therefore, the applicability of these simulation results for decisionmaking in many developing countries is limited. Still, in countries with high enrollment of female primary school children, DT immunization may prove to be highly cost-effective for tetanus prevention, especially when it is an incremental measure in an integrated primary health care strategy (which may at the same time include vitamin A distribution, administration of anthelmintics, and screening for trachoma).

Single-dose tetanus toxoid vaccine which would confer lifelong immunity is likely to become available for human use within five to ten years. Testing in animals has already begun, with testing in humans expected soon. Funds may be needed in the future to support trials in humans. The vaccine would contain biodegradable microcapsules of different thicknesses which would slowly release tetanus toxoid over a prolonged period. Administered early in life, the vaccine would provide protection for the individual and for future pregnancies. Although unit costs per dose of this vaccine cannot be predicted, it is unlikely to be expensive. The single-dose vaccine would also significantly reduce the number of required immunization contacts, resulting in significant cost savings. This same biotechnology relying on impregnated microcarriers may be useful for delivering other inactivated vaccines.

Pregnant women and those of childbearing age are frequently not screened and immunized with tetanus toxoid when they come into contact with the health system for whatever reason. The World Health Organization recommends immunization of eligible women and infants at every encounter with the health system in order to reduce missed opportunities. Immunization of pregnant women during routine prenatal care visits as early as possible during pregnancy and immunization of women of childbearing age at childhood immunization sessions should lead to reduced costs of the immunization program by substantially increasing efficiency (WHO/EPI 1988b).

Routine immunization of women either is conducted through antenatal clinics and MCH services or is the responsibility of EPI. Where possible, routine TT immunization (and mass immunization strategies) should be designed as integrated efforts with MCH services. If TT immunization is given as part of an integrated package with childhood immunization and prenatal care services, the cost is likely to be reduced.

The World Health Organization has recommended expanding the target population for tetanus toxoid immunization from pregnant women to all women of childbearing age (WHO/EPI 1986). Initially, there was concern that enlarging the population would not be an affordable strategy for developing countries. Gérard Foulon investigated the incremental cost of implementing a five-dose schedule for all women of childbearing age (personal communication, July 12, 1990). He found that total costs would increase within the first five years of adopting this strategy but would then revert to preexpansion costs. If the incremental costs of additional vaccine, storage, training, and monitoring could be financed through donor resources, this policy would not represent an economic burden to developing countries in the short run.

To the extent that parents will quickly replace their lost baby, a death from NNT will continue to exact incalculable costs within the family. In the absence of lactational amenorrhea following a baby's death from NNT, the mother may well become pregnant sooner. Shorter pregnancy intervals are associated with higher infant and child mortality. Even if the older child dies in infancy, too short a birth interval still places the younger child at very high risk. Another pregnancy so soon also jeopardizes the health of the mother.

The REACH project determined that half of immunization costs (capital and recurrent) in developing countries are currently financed by external resources from donor organizations (Brenzel 1989). Tools for making resource allocation decisions, such as cost-effectiveness analyses, have not been used often in cases where resources are abundant. Sustaining immunization coverage gains, however, is becoming a greater priority for program managers, and this translates into selecting the most affordable and effective strategies for tetanus prevention. The estimates calculated in this chapter underscore the need for continued donor assistance in the financing of TT immunization programs, given the economic declines and growing populations faced by most developing countries.

Case Management of Tetanus

This section discusses strategies for the treatment of tetanus and their costs and benefits.

Case Management Strategies

Much of the following discussion on case management of NNT and non-NNT is based on an authoritative essay entitled "Treatment of Tetanus" (Rey, Diop-Mar, and Robert 1981), to which the reader is referred. Death from tetanus commonly occurs in association with spasms, which lead to acute asphyxia. Treatment is largely symptomatic and attempts to prevent and counteract the effects of spasticity and spasms on respiration. Improvements over the past few decades in methods of neurorespiratory resuscitation and use of specialized intensive care units have led to improved outcomes. Nevertheless, even treated tetanus remains extremely serious with the course and prognosis dependent on age, preexisting conditions, superimposed infections and complications of treatment, and availability of medical facilities with advanced equipment and expert staff (Veronesi and Focaccia 1981).

Expert use and timing of sedatives, muscle relaxants, and respiratory assistance (including tracheotomy and artificial ventilation, if indicated) are typically required, but these procedures carry their own iatrogenic risk. Inaccessibility of specialized treatment facilities in much of the world results in delayed admission, a factor associated with increased mortality.

Treatment of NNT and non-NNT patients consists of excising, cleansing, and disinfecting the wound; antibiotic therapy; use of benzodiazepines for their sedating, anticonvulsant, and muscle-relaxing properties; maintenance of effective ventilation, particularly by tracheotomy; parenteral administration of human tetanus immune globulin or antitetanus serum of equine origin, which is less desirable because of frequent adverse side effects; maintenance of water, electrolyte, and nutritional balance; and intensive nursing care. (Neonates in particular require assisted respiration in specialized neonatal intensive care units.) The effectiveness of this symptomatic treatment depends on financial and human resources rarely available where tetanus most frequently occurs.

Following the treatment outline above, hospitals in France and Japan have recorded impressive reductions in fatality of non-NNT patients to a rate of approximately 10 percent despite the increasing age of patients in recent years (Rey, Diop-Mar, and Robert 1981; Ebisawa and Homma 1986). The principal determinant of survival in Japan was admission to an intensive care unit where staff, including anesthesiologists, were trained in treatment of tetanus. After 1974, gastrointestinal and cardiac complications overtook respiratory insufficiency with or without pulmonary infection as the leading cause of death for Japanese tetanus patients. Rey, Diop-Mar, and Robert (1981) report that intensive care of newborns has in a few instances even reduced neonatal fatality to 10–20 percent from 90 percent, although the risk of incapacitating sequelae has increased owing to survival after intensive care.

Rey, Diop-Mar, and Robert (1981) suggest that in developing countries a compromise between modern medical advances and available resources is needed. They advocate establishment of special care units in facilities admitting more than 100 cases per year. Such a unit would admit other patients also requiring continuous monitoring.

Practically, the financial and human resources which they recommend for tetanus patients may still be out of reach for most developing countries: one doctor continuously available; two daytime nurses and one nighttime nurse, which would require a team of six to eight trained nurses; several orderlies; oxygen; apparatus for aspiration, intravenous infusion, catheterization of veins or bladder, and tracheotomy; nasogastric tubes; and appropriate sedatives, antibiotics, and serum. Laboratory tests, bacteriological examinations, and air conditioning are desirable but may have to be omitted.

Even with relatively simple and inexpensive treatment, it is in the newborn that the most noticeable improvement in survival rate is found (Rey, Diop-Mar, and Robert 1981). Schofield (1986) observes, however, that with routine treatment an overall fatality reduction of only 10 percent can be expected. Even in the United States as recently as 1953–61, the case-fatality rate for all tetanus remained as high as 63 percent (Bytchenko 1966). In the absence of sophisticated equipment and the most advanced drugs, the quality and continuity of nursing care, which allows early recognition and treatment of potentially life-threatening complications, is probably the most important factor when case fatality varies greatly from place to place (Barten 1969).

Cost and Benefits of Treatment

There have been some attempts to examine the costs and benefits of treatment of tetanus compared with prevention though immunization. Treatment costs are more relevant for non-NNT, since NNT cases are rarely brought to the hospital and the case-fatality rate of NNT approaches 100 percent. Cvjetanovic and others (1972) state that treatment costs may vary from $50 to $900 ($148 to $2,665), with an average of $200 per case ($592) in developing countries.[3] Rey, Guillaumont, and Majnoni d'Intignano (1979) estimate treatment costs from $15,000 to $20,000 ($28,500 to $38,000) per case in the United States and $10,000 to $16,000 ($19,000 to $30,500) in France. Berggren (1974a) estimates treatment costs of $12 ($30) per day at Albert Schweitzer Hospital in Haiti, with an average of seventeen days of treatment. Rey and Tikhomirov (1989) report a mean hospital stay for non-NNT patients of sixteen days, though a significant proportion of cases die within the first two or three days. Griffith and Sachs (1974) report a mean hospital stay in Ludhiana, India, of eighteen and one-half days and a direct daily cost of 991 rupees ($226). When only surviving patients are considered, a total of 1,857 rupees ($423) were spent to treat each infant.

Table 9-8 provides treatment costs per case of tetanus (NNT and non-NNT) in various locales. It must be emphasized that treatment protocols (use of drugs, ATS, tetanus immune globulin, ventilation, and so on) are not uniform and that cost methodologies vary; therefore, comparison of these estimates is not straightforward. Nevertheless, with a median cost per NNT death averted of $110 by means of TT immunization (table 9-7), prevention of tetanus is by far more cost-effective than treatment. Cvjetanovic and others (1972) estimated that cumulative savings in treatment costs over the course of thirty years would exceed by a factor of more than 2.5 to 1 the cost of continuous immunization of pregnant women. Costs associated with passive immunization as part of wound management would also decrease as the population becomes protected by TT. Berggren (1974a) calculated that more than 50,000 hospital days were saved over a four-year period by Haiti's vigorous tetanus immunization program, which allowed a redistribution of $600,000 worth of care from tetanus to other priorities. He estimated a benefit-to-cost ratio of 9 to 1.

Table 9-8. *Costs Per Capita of Tetanus Treatment and Immunization in Selected Areas*
(1989 U.S. dollars)

Location	*Type of case*	*Cost of treatment*	*Cost of vaccination*
Argentina	Average	160–2,553	0.80
India (Delhi, Safdarjang Hospital)	Average	319	—
Iran, Islamic Rep. of	Government hospital	319–807	1.00
	Private hospital	957–2,042	6.40–10.50
Senegal (Dakar)	Fatal	255–511	0.90–1.80
	Surviving	460–2,374	
	Average	638–766	
Yugoslavia	Simple	287	0.30–1.60
	Artificial respiration required	2,872	
Developing countries	Average	319–957	1.00–1.60

— Data not available.
Note: All costs have been converted into 1989 U.S. dollars, assuming costs in original studies were in 1970 dollars.
Source: Cvjetanovic, Grab, and Uemura 1978.

Rey, Guillaumont, and Majnoni d'Intignano (1979) estimate the costs of alternative immunization strategies and benefits in treatment costs saved over a thirty-year period (see table 9-9) based on the model developed by Cvjetanovic and others (1972). Assuming that the cost per vaccination is $1.18 (all costs have been converted to 1989 U.S. dollars) and the treatment cost for one case is $592, they calculate that continuous vaccination of pregnant women would result in the lowest cost per case averted ($245), compared with one mass vaccination campaign ($463 per case averted), repeated mass campaigns ($595), and a combination of repeated mass campaigns and continuous vaccination ($468). This model does not, however, examine costs of continuous (routine) immunization of all women of childbearing age.

This information on the costs of treatment of non-neonatal tetanus can be used to estimate the cost-effectiveness of case management.[4] The range of treatment costs for developing countries cited in table 9-8 is from $319 to $957. Footnote b of table 9-1 indicates that treatment in hospitals of non-neonatal tetanus cases may reduce the case-fatality rate by 15 to 20 percentage points. Dividing the cost of treatment by this change in CFR gives a range in estimated cost per death averted of $1,595 to $6,380. As mentioned above, Cvjetanovic and others (1972) estimate an average cost of $592 per case treated in developing countries, resulting in a cost per death averted of $2,960 to $3,947, depending on the assumed reduction of 15 to 20 percentage points in the CFR. Thus, treatment of non-neonatal tetanus appears to be substantially less cost-

Table 9-9. Cost-Benefit and Cost-Effectiveness of Various Immunization Programs in Developing Countries over a Thirty-year Period
(1989 U.S. dollars)

Immunization program	*Cumulative cost*	*Number of cases averted*	*Treatment cost saved*	*Cost per case averted*
None[a]	n.a.	n.a.	n.a.	n.a.
One mass campaign[b]	592,288	1,278	756,944	463
Repeated mass campaigns at ten-year intervals[b]	2,194,391	3,686	2,183,173	595
Continuous vaccination of pregnant women[c]	1,513,761	6,184	3,662,708	245
Combination of repeated mass campaigns and continuous vaccination of pregnant women	3,708,152	7,922	4,692,105	468

n.a. Not applicable.

Note: Assumes population of one million at beginning of the period; thereafter, annual growth rate is 2 percent. Cost of one vaccination is $1.18; treatment cost for one case is $592.

a. Without immunization program, incidence would be 400 per 100,000 newborns and 18 per 100,000 population.

b. Assumes coverage of 50 percent, vaccine effectiveness of 95 percent.

c. Assumes coverage of 90 percent, vaccine effectiveness of 95 percent.

Source: Rey, Guillaumont, and Majnoni d'Intignano 1979, based on Cvjetanovic and others (1972).

effective than prevention. Prevention should therefore remain the intervention of top priority.

Non-NNT is important from an economic perspective in that treatment costs are high, death is common, long-term disability may ensue, and prolonged illness may result in lost productivity for the family and society (Rey, Guillaumont, and Majnoni d'Intignano 1979). Age-distribution data from studies conducted in Bombay (1954–79) and Dakar (1960–86) indicate that a high proportion of deaths and between 50 and 60 percent of non-NNT cases occur among the economically productive groups age ten to fifty-nine years (Rey, Guillaumont, and Majnoni d'Intignano 1979).

With increasing immunization of infants and older children with DPT and DT, an epidemiological shift in incidence to older age groups is expected to continue. These epidemiological shifts will have an effect on the economic productivity of developing societies.

The annual cost fully to protect the entire adult population of the developing world is difficult to estimate because vaccinations administered in past years may still be protective. Unlike infants (a cohort which renews itself annually and is consequently easily calculated), women receive multiple doses of TT at varying intervals over a thirty-year reproductive span; and women enter and leave the eligible age range continuously (Steinglass 1990). Still, assuming a cost of $0.91 per dose of TT (table 9-7), a five-dose schedule for lifelong protection, and a total adult population of 2.4 billion, we arrive at a cost of approximately $10.9 billion to protect this population for life against tetanus and their offspring against NNT. This figure is less than the total potential savings resulting from avoided economic loss, avoided treatment, and prevention of disability. The cost to protect all unimmunized women of childbearing age would be less than half this amount and would eliminate NNT and reduce adult tetanus by half.

The estimates of tetanus deaths can be used to project crude cost-effectiveness figures for prevention of adult tetanus cases.[5] Murray, Yang, and Qiao (1992) estimate that 10.6 million deaths occur annually in developing countries in the adult age group (fifteen to fifty-nine years of age). From tables 9-1 and 9-2 earlier in this chapter, we can estimate that 132,500 (1.25 percent) of these deaths are due to tetanus. An individual in a developing country has approximately a 24 percent chance of dying of any cause between the ages of fifteen and fifty-nine (Murray, Yang, and Qiao 1992). By derivation, an adult in a developing country has approximately a 0.3 percent chance of dying of tetanus between those ages.

Full immunization by the age of fifteen (through a combination of DPT, DT, Td, and TT during infancy, at school, and during other contacts with the health system) would require five properly spaced shots and would most likely fully protect an individual from the risk of tetanus for life.

Unfortunately, few of the studies reviewed earlier included examinations of the cost of providing tetanus as a part of infant and school immunization programs. For the most part, they focused on reaching adult women in order to prevent neonatal tetanus deaths. The marginal cost of providing the "T" in DPT is likely to be very small, and the costs of providing DT or Td to schoolchildren might be substantially different from the costs of providing TT to pregnant women. Nevertheless, the median cost per TT dose of $0.91 (table 9-7) is the most reasonable estimate we have available of the unit cost of delivering tetanus immunization. If five doses were provided at a median cost of $0.91 per dose, full protection could be bought for $4.55.

If this cost is divided by the individual risk of an adult dying of tetanus between the ages of fifteen and fifty-nine (0.3 percent), we can derive a cost per death averted of $1,517. This cost of preventing adult tetanus is nearly fourteen times higher than the median cost per NNT death averted ($110) found in table 9-7, but it compares well with other adult interventions discussed elsewhere in this collection.

Research Agenda for the 1990s

A review of the recent literature has identified a research agenda for the 1990s. Such a lengthy list is not meant to suggest that current control efforts should await research findings. Enough is already known about the benefits of NNT control efforts to justify vigorous implementation at country level. The research agenda includes topics in vaccinology, epidemiology, programmatic concerns, and behavioral science.

Vaccinology

- Determine the nature, action, and duration of immunity from primary and reinforcing doses of TT with varying potencies and intervals in different settings (Jones 1983).
- Define the effect of the varying levels of maternal tetanus antitoxin on the level and duration of infant tetanus antitoxin following varying doses of DPT (WHO/EPI 1989b).
- Develop and test a TT vaccine which is more immunogenic with fewer doses, such as a single-dose high-potency TT with pulsed or continuous release of toxoid, with or without adjuvants, that uses alternative polymers as the vehicle (Galazka 1983; WHO/EPI 1989a).

Operational Strategies

- Identify and implement alternative cost-effective NNT prevention strategies in a variety of settings (including hard-to-reach areas), identify costs and operational constraints, and document the effect on immunological status and NNT incidence. Such strategies include expanding the TT schedule to five doses and the target groups to all women of childbearing age, immunizing at every contact with the health services, offering immunization at markets, immunizing schoolchildren in the early grades, launching mass campaigns every five or ten years, incorporating TT in national vaccination days, enforcing compulsory TT before marriage certificates are issued, scheduling a routine dose of TT at the start of every decade of life—at ages ten, twenty, thirty, and forty.
- Determine practical methods of screening and immunizing all women of childbearing age on every contact with the health services.
- Determine methods of identifying and routinely immunizing women entering the childbearing age.
- Explore potential use of TT outside the cold chain, including the possibility of administration by prefilled single-use injection devices which can be used by peripheral workers—for example, TBAs or village health workers (WHO/EPI 1989a; WHO/EPI 1989b).
- Study use, distribution, and effect of disposable delivery kits in a variety of settings.

Monitoring

- Develop and apply valid criteria, guidelines, operational indicators, and methodologies to monitor levels of TT coverage and protection, clean delivery, and cord care (Steinglass 1988; WHO/EPI 1989b).
- Review experience using lifetime home-based records and develop several record-keeping options for TT protection in areas employing different NNT prevention strategies. Study factors for promoting retention of records by the public.
- Include in the standard thirty cluster community surveys of immunization coverage questions on maternal TT status, age and parity of mother and protection status of delivery, number of prenatal care visits, place of delivery and attendant, and circumstances of delivery.
- Include TT in surveys on missed opportunities for immunization to determine magnitude and correction of problem.
- Conduct serological (gold-standard) assessments of immunologic and immunization status in the community as part of NNT mortality and thirty cluster coverage surveys (Schofield 1986).

Surveillance

- Develop various methods of identifying high-risk population subgroups and areas for focused interventions.
- Determine the magnitude of maternal mortality due to tetanus.
- Determine the feasibility of community-based surveillance and reporting of NNT cases and the utility of case investigations.
- Determine methods of documenting the absence of NNT as part of the elimination effort.
- Determine in selected areas the relationship of altitude to NNT incidence to concentrate control activities in high-risk areas.

Impact Evaluation

- Assess sustained effect of TBA training on changing delivery and cord care practices and on NNT and neonatal mortality in "before" and "after" control and experimental areas (Ross 1986a).
- Conduct retrospective case-control studies of the effect of TBA training (and TT immunization) on neonatal mortality and NNT in areas where some TBAs have been trained and others have not (Ross 1986b).
- Conduct studies on the incremental effect of TBA training, above that achieved by TT immunization alone, on NNT and neonatal mortality (Ross 1986b).

Social Factors

- Review experiences of the use of techniques of social marketing and social mobilization directed at the problem of NNT.
- Conduct market research and practical behavioral research on immunization acceptability, intrapartum and postpartum care, and cultural perceptions of NNT to identify and overcome resistance on the part of the public and providers and to promote TT immunization and clean delivery practices (Bastien 1988; Pillsbury 1989).

- Study methods of community involvement for routine identification and referral of females for TT, including use of TBAs, women's groups, political structure, and religious leaders.

Cost-Effectiveness

- Study the cost and cost-effectiveness of alternative NNT control strategies, especially TT immunization of all women of childbearing age and TBA training. Study the logistical implications and resource requirements for widened immunization target groups, so as to influence local decisions on resource allocation.
- Refine simple costing guidelines on alternative NNT prevention strategies for use by program managers for decisions on resource allocation.

Conclusions

Tetanus kills 750,000 babies annually, and non-NNT kills an additional 120,000 to 300,000 persons. Neonatal tetanus is completely preventable by means of maternal immunization with tetanus toxoid or aseptic care of the umbilical cord. Prevention of NNT will reduce neonatal mortality by up to half and infant mortality by up to one-quarter in unimmunized populations. Increasingly, the level of NNT is being recognized as a barometer of the health status and well-being of mothers and newborns, with each case attesting to multiple failures of the health system (Galazka and Cook 1985).

Prevention of NNT should be a priority for resource allocation in many developing countries, given the magnitude of the disease (high incidence rates in poorer countries), the severity of the disease (high case-fatality rates even with treatment), the high cost of treatment, and the availability of a safe, highly efficacious, and cost-effective vaccine.

The strategies chosen for immunization, as well as the target groups, should be defined locally and will depend on a number of different factors, including:

- Level of incidence
- Level of resources available (nationally and from donors)
- Organization and utilization of health services (particularly preventive and MCH services)
- Existence of other channels for contact (schools, bride registration, TBAs, and so on)
- Immediacy of desired effect (use of campaigns or routine immunization)
- Cost-effectiveness and opportunity cost of other health interventions and strategies
- Incremental cost of different TT strategies
- Operational and behavioral considerations

As was demonstrated by the studies in Deschapelles, Haiti (Berggren, 1974a), and Pidie District, Indonesia (Berman and others 1991; WHO/EPI 1988a), mass campaigns can be effective in rapidly reducing the backlog of unimmunized individuals in the target population. Continuous immunization through routine services is a more common approach and will be necessary in most cases to ensure continued protection of the population over time. In the cost studies reviewed, the median cost per NNT death averted was $110.

As Berman and others (1991) noted: "The appropriate agenda for planning is not an absolute choice amongst different strategies, but a flexible schedule for how different approaches can be combined over time to maximize results at an affordable cost. This approach was suggested by Cvjetanovic et al. (1972) and still remains valid."

The World Health Organization now recommends efforts to eliminate NNT worldwide by 1995. Achievement of this global target will require a global commitment of resources and mobilization of political will at all levels. Unlike other eradication and elimination efforts (for example, smallpox and polio), there can be no cessation of vaccination and revaccination efforts once NNT elimination is achieved, because the infective agent exists in the environment and cannot be eradicated. Elimination itself will need to be sustained forever by means of active immunization. Neonatal tetanus is easily preventable and can be eliminated as a public health problem in most countries at a reasonable cost. This cost would be affordable for most countries, although many of the poorer countries (which also tend to have the largest tetanus problem) will require donor assistance for years into the future.

Appendix 9A. Cost-Effectiveness of Tetanus Immunization Programs

Two of the following four tables examine the cost-effectiveness of tetanus immunization programs from the standpoint of epidemiologic data, cost, and effectiveness data. The other two tables use the same data to examine simulation models of cost-effectiveness.

Table 9A-1. Studies of Cost-Effectiveness of Tetanus Immunization Programs: Epidemiologic Data

Location (source)	Intervention year	Strategy	Target group	Population total	Population Target	Number of TT immunizations given: One	Two	Three or more	Total	NNT incidence rate[a]	NNT mortality rate[a]	Case-fatality rate
Burkina Faso (de Champeaux and Martin 1989)[b]	1987	Fixed centers	Women 15–44	—	—	6,043 13,832	1,957 5,928	0 0	8,000 19,760	—	—	—
Cameroon (Brenzel 1987)	1987	Mass campaign	Women 15–49	—	—	—	—	—	151,415	—	—	—
Ecuador (Shepard and others 1987)	1974–85	Fixed centers	Pregnant women	—	—	—	—	—	179,765	—	—	—
The Gambia (Robertson and others 1985)	1980–81	Fixed centers and outreach	Pregnant women nationwide	—	—	—	84 percent	—	—	—	40 in unimmunized (1965)	90 percent (1982)
Haiti/ Deschappelles (Berggren 1974a,b)[c]	1967–71	Mass	Females ten and older	94,000	—	247,677	213,002	178,327	639,006	64 (1967)	60 (1966)	85 percent[d]
		Marketplace	All people ten and older	—	—	—	—	—	—	9 (1972)	—	—
		Rally posts	Children									
Haiti (Narcisse 1989)	1988	Fixed centers	Women 15–44	—	—	—	—	—	165,713	—	—	—
		Mass campaign	Women 15–44	—	—	—	—	—	542,461	—	—	—
		Rally posts	Women 15–44	—	—	—	—	—	165,713	—	—	—
		Horse teams	Women 15–44	—	—	—	—	—	127,496	—	—	—
India/Narangwal (Kielmann and Vohra 1977)[e]	1972–73	Campaign	Women 15–44	13,000,000	1,820	1,583 (87 percent)	0	0	1,583	—	25	—
Indonesia/Central Java (WHO/EPI 1981b)[f]	1979–80	Fixed centers and outreach	Pregnant women	1,400,000 two rural sites	—	—	—	—	—	—	—	—
Indonesia/Central Java (Barnum, Tarantola, and Setiady 1980)[f]	1979–84	Fixed centers and outreach	Children Pregnant women	—	—	—	—	—	—	—	—	—
Indonesia/Pidie (WHO/EPI 1988; 1988a; Berman and others 1991)[g]	1985	Mass campaign	Women 10–45	380,000	95,300	83,642 (88 percent)	67,962 (71 (percent)	—	151,604		Provincial: 20.9 (1984)[d] Pidie (5 clusters): 32.1 ± 15 (1984) Pidie (30 clusters): 4.9 ± 2.6 (1987)	85 percent[d]

(Table continues on the following page.)

Table 9A-1 (continued)

Location (source)	Intervention year	Strategy	Target group	Population total	Population Target	Number of TT immunizations given: One	Two	Three or more	Total	NNT incidence rate[a]	NNT mortality rate[a]	Case-fatality rate
Indonesia/Aceh (Berman and others 1991)[h]	1985	Fixed centers	Pregnant women in four sub-districts	—	358	—	43	—	—	—	—	85 pecent[d]
				—	462	—	97	—	—	—	—	
				—	732	—	205	—	—	—	—	
				—	2,435	—	1,948	—	—	—	—	
Indonesia/Central Lombok (UNICEF 1985)[i]	1985	Campaign	All women of reproductive age	577,000	140,000	129,728 (93 percent)	125,982 (90 percent)	—	255,710	—	Seven clusters: 28 ± 9.7 (1983) Provincial level: 16.7	85 percent[d]
Senegal/Dakar (Rey and others 1979)[j]	1970	Mass campaign (two times) (hypothetical)	Total population	650,000	650,000	—	—	—	—	300/650,000	100/650,000	30–40 percent
	1970–73	Mass campaign (seven times) (real data)	Total population	650,000	650,000	—	—	—	—	—	—	—
Senegal (Brenzel and others 1987)	1987	Mass campaign	Pregnant women	—	—	—	—	—	71,546	—	—	—
Sudan (Brenzel and others (1987)	1988	Fixed centers and mobile teams	Pregnant women	—	190,120	40,686	23,575	—	64,261	—	—	—
			Pregnant women	—	180,177	69,548	45,405	—	114,953	—	—	—
			Pregnant women	—	119,556	68,864	60,854	—	129,718	—	—	—
			Pregnant women	—	920,030	332,131	231,848	—	563,979	—	—	—
Thailand (Phonboon and others 1989)[k]	1987	Fixed centers and outreach	Pregnant women	3,025,000	—	—	42–70 percent	—	—	—	—	—

— Not available.

a. Per 1,000 live births unless otherwise noted.

b. In Yako, EPI used oral polio vaccine and DPT. In Gourcy, EPI used DPTP (DPT with injectable polio).

c. Three doses of TT one month apart; minimum five years protection. Numbers of TT immunizations derived from information in cited document. Incidence based on hospital admissions. Mortality estimate rom retrospective community survey. Calculations use actual program intervention data.

d. WHO estimate of case-fatality rate.

e. Assumes lifelong immunity from one dose of high-potency (30Lf/ml) calcium phosphate-adsorbed TT with 80 percent efficacy.

f. Uses hypothetical model of incidence.

g. Two doses of TT. Coverage figures differ slightly by source.

h. Hypothetical incidence data. Targets derived from information reported in document.

i. Two doses of TT. Previous vaccination history ignored.

j. Hypothetical study of ten-year program of TT2. Low CFR due to high proportion of cases in people over one year of age.

k. Two doses of TT.

Source: See first column of this table.

Table 9A-2. Studies of Cost-Effectiveness of Tetanus Immunization Programs: Cost and Cost-Effectiveness Data

			Total Cost		Cost per TT dose		Cost per TT2		Cost per case prevented[a]		Cost per death averted[a]	
Location (source)	*Subdivision*	*Year*	*Current dollars*	*1989 dollars*	*Current dollars*	*1989 dollars*	*Current dollars*	*1989 dollars*	*Current dollars*	*1989 dollars*	*Current dollars*	*1989 dollars*
Burkina Faso (de Champeaux and Martin 1989)[b]	Gourcy	1987	11,568	12,607	0.59	0.64	1.95	2.13	—	—	—	—
	Yako		7,447	8,116	0.93	1.01	3.81	4.15	—	—	—	—
Cameroon (Brenzel 1987)[b]	n.a.	1987	186,218	202,955	1.23	1.34	3.82	4.16	—	—	—	—
Ecuador (Shepard and others 1987)[b]	n.a.	1985	62,918	72,482	0.35	0.40	—	—	—	—	—	—
The Gambia (Robertson and others 1985)[c]	n.a.	1980	125,315	188,463	1.05	1.58	3.48	5.23	136.36	205.07	151.53	227.89
Haiti/Deschapelles (Berggren 1974a,b)[d]	n.a.	1969	67,000	226,346	0.10	0.34	0.31	1.05	28.88	97.57	33.98	114.79
Haiti (Narcisse 1989)[b]	n.a.	1988	143,926	150,867	0.87	0.91	—	—	—	—	—	—
			888,990	931,862	1.63	1.71	—	—	—	—	—	—
			32,846	34,430	0.20	0.21	—	—	—	—	—	—
			138,890	145,588	1.09	1.14	—	—	—	—	—	—
India/Narangwal (Kielmann and Vohra 1977)[e]	Initial period	1972	253,846	751,750	0.10	0.29	—	—	—	—	32.85	97.27
	Maintenance phase		n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.12	0.34
Indonesia/Central Java (WHO/EPI 1981b)[f]	n.a.	1980	—	—	0.62	1.18	2.06	3.92	—	—	—	—
Indonesia/Central Java (Barnum and others 1980)[f]	n.a.	1978	32,800,000	62,352,475	—	—	—	—	8.70	16.54	135.00	256.63
Indonesia/Pidie (WHO/EPI 1988a; Berman and others 1991)[g]	n.a.	1985	108,355	124,825	0.71	0.82	1.59	1.84	106.25 (92–127)	122.40 (106–146)	125.00 (108–147)	144.00 (124–179)
Indonesia/Aceh (Berman and others 1991)[h]	Tanah Pasir	1985	82	94	—	—	1.91	2.20	77.38	89.15	91.04	104.88
	Samudera		233	268	—	—	2.40	2.76	97.90	112.78	115.18	132.69
	Matangkuli		261	301	—	—	1.27	1.47	51.98	59.88	61.15	70.45
	Jeumpa		1,114	1,284	—	—	0.57	0.66	23.34	26.89	27.46	31.64
Indonesia/Central Lombok (UNICEF 1985)[i]	NNT mortality, 28.0	1985	50,000	57,600	0.20	0.23	0.40	0.46	38.43	44.27	45.21	52.09
	NNT mortality, 18.3	—	—	—	—	—	—	—	58.80	67.74	69.18	79.69
	NNT mortality, 37.7	—	—	—	—	—	—	—	28.54	32.88	33.58	38.68
	NNT mortality, 16.7	—	—	—	—	—	—	—	64.44	74.23	75.81	87.33

(Table continues on the following page.)

Table 9A-2 (continued)

Location (source)	Subdivision	Year	Total Cost: Current dollars	Total Cost: 1989 dollars	Cost per TT dose: Current dollars	Cost per TT dose: 1989 dollars	Cost per TT2: Current dollars	Cost per TT2: 1989 dollars	Cost per case prevented[a]: Current dollars	Cost per case prevented[a]: 1989 dollars	Cost per death averted[a]: Current dollars	Cost per death averted[a]: 1989 dollars
Senegal/Dakar (Rey and others 1979)[j]	Hypothetical	1970	—	—	—	—	—	—	175.00	558.45	528.00	1,684.92
	Real data	1971	70,000	214,468	—	—	—	—	269.23	824.88	897.44	2,749.59
Senegal (Brenzel and others 1987)[b]	n.a.	1987	49,786	54,261	0.70	0.76	—	—	—	—	—	—
Sudan (Brenzel and others 1990)[b]	Darfur	1988	108,065	113,277	1.68	1.76	4.58	4.80	—	—	—	—
	Kordofan		93,776	98,298	0.82	0.86	2.07	2.16	—	—	—	—
	Capital		164,819	172,768	1.27	1.33	2.71	2.84	—	—	—	—
	National level		929,577	974,406	1.65	1.73	4.01	4.20	—	—	—	—
Thailand (Phonboon and others 1989)[b]	Hospitals	1985–86	—	—	—	—	8.90	10.25	—	—	—	—
	Health centers		—	—	—	—	10.30	11.87	—	—	—	—

— Not available.
n.a. Not applicable.
a. NNT only, unless otherwise specified.
b. Calculated from cost-effectiveness study of entire EPI.
c. Cost of expatriate personnel excluded. Costs based on three contacts required to receive TT3 (three of eight contacts = 37.5 percent of total costs).
d. Total cost is expenditures only. Cost per case and death averted excludes another 630 non-NNT cases prevented. If these were included, the cost per case prevented would fall to $23 ($77 in 1989 dollars), and the cost per death averted would drop to $29 ($99 in 1989 dollars).
e. Hypothetical cost data for 2.6 million women age fifteen to forty-four.
f. Range in cost per TT = $0:56–$0.76; range in cost per TT2 = $1.43–2.61. Cost data include five years' cost of DPT and TT and cases and deaths from diphtheria, pertussis, and tetanus.
g. Cost per TT dose and case prevented derived from information reported in cited documents. Applying upper and lower confidence intervals (17–47) around 32.1/1,000 in five clusters of 1984 survey in Pidie and 2.3–7.5/1,000 in thirty-cluster survey in 1987, cost per death averted ranges from $45–$211 ($52–$243) in 1989 U.S. dollars.
h. Cost per case and death prevented does not take into account the protective effect of TT2 on all deliveries within three years. Cost per case prevented data derived from information reported in cited document.
i. Cost excludes administrative salaries at national level. Cases and deaths averted estimated from data reported in cited document, assuming vaccine efficacy of 95 percent; general fertility rate of 110/1,000; average duration of protection of three years.
j. Total costs include only vaccine costs. Costs for second study, using real data, were likely incurred over entire four-year period. Authors assume cost year is 1971.
Source: See first column of this table.

Table 9A-3. *Simulation Models of Cost-Effectiveness of Tetanus Immunization Programs: Epidemiologic Data*

				Population		*TT coverage*				
Source	*Location*	*Strategy*	*Target group*	*Total*	*Target*	*TT1*	*TT2*	*NNT incidence*[a]	*NNT mortality*[a]	*Case-fatality rate*
Cvjetanovic and others 1972[b]	—	Mass campaign	Total population	1,000,000	1,000,000	—	—	4 Neonatal	—	With treatment:
		Repeated mass campaign (3x)	Total population	1,000,000	1,000,000	—	—	18/100,000 (adult)	—	80 percent general 30 percent newborn
		Continuous pregnant	Pregnant women	1,000,000	1,000,000	—	—		—	Without treatment: 90 percent general
		Continuous preg-nant and repeated mass (3x)	Pregnant women and total population	1,000,000	1,000,000	—	—		—	40 percent newborn
Kessel 1984[c]	—	Preschool	Children	—	—	—	—	—	10–30	—
		Primary school	Children	—	—	—	—	—	—	—
		Antenatal TT	Pregnant women	—	—	—	—	—	—	—
		Antenatal outreach	Pregnant women	—	—	—	—	—	—	—
Sharma and Sharma 1984a,b[d]	India/rural Uttar Pradesh	Continuous (50–80 percent)	Pregnant women	—	—	—	—	Adult: 185/100,000	—	Adult: 50 percent
			Children 5–10 Children 10–15 Children < 5	—	—	—	—	Neonatal: 68.8	66.7	Rural: 97 percent
		Mass—repeated every five years (50 percent coverage)	Women 15–44 All adults							
Smucker and others 1984[e]	India/Uttar Pradesh (2 districts)	Campaign (teams) every 5 years	Women 10–44	3,529,048	882,262	75–95 percent	60–90 percent	—	53	—
		Outreach (continuous)	Women 10–44	3,529,048	882,262	75–95 percent	60–90 percent	—	53	—

— Not available.

a. Per 1,000 live births unless otherwise indicated.

b. Includes NNT and not NNT. Assumes 50 percent coverage for campaign and 90 percent coverage for continuous strategy. Booster given one year after TT2. Thirty-year time horizon.

c. Excludes cases and deaths from non-NNT.

d. Vaccine efficacy is 90 percent, twenty-five year time horizon, two TT per woman. Boosters given every five years. NNT mortality from sample of 3,267 births. Excludes cases and deaths from non-NNT. Intervention year 1978.

Table 9A-4. Simulation Models of Cost-Effectiveness of Tetanus Immunization Programs: Cost and Cost-Effectiveness Data

Source	Location	Cost year	Total cost		Cost per TT dose		Cost per TT2 dose		Cost per case prevented[a]		Cost per death averted[a]	
			Current dollars	1989 dollars	Current dollars	1989 dollars	Current dollars	1989 dollars	Current dollars	1989 dollars	Current dollars	1989 dollars
Cvjetanovic and others 1972[b]	—	1972	—	—	—	—	—	—	156.50	463.47	—	—
									201.00	595.25	—	—
									82.70	244.91	—	—
									158.10	468.20	—	—
Kessel, 1984[c]	—	—	—	—	Uses hypothetical financial units, not actual dollars. Concludes that school-based immunization is most economical for long term complementary strategy.						—	—
Sharma and Sharma 1984[a,b]	India/rural Uttar Pradesh[c]	—	—	—	Favors continuous immunization of pregnant women. Mass immunization leads to short-lived declines in cases and deaths.						—	—
Smucker and others 1984[d]	India/Uttar Pradesh (2 districts)	1978 (?)	1,147,795	2,181,947	0.70	1.34	1.44	2.74	—	—	3.55	6.75
			1,461,477	2,778,443	1.23	2.33	2.76	5.25	—	—	6.24	11.86
			431,222	819,749	0.26	0.50	0.54	1.03	—	—	1.36	2.59
			613,517	1,166,290	0.52	0.98	1.16	2.20	—	—	2.56	4.87

a. Cost per case and death averted is for NNT only, unless otherwise specified.
b. No discounting of costs and benefits.
c. Gives rankings of cost per prevented death at different NNT mortality rates. Makes assumptions regarding ranking of financial units and strategies.
d. First line for each strategy: most cost-effective scenario. Second line for each strategy: least cost-effective scenario costs for twenty-five year period discounted at 12 percent per year; deaths not discounted.

Notes

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1. The term "economic costs" refers to the value of all resources used, including those which were donated and those for which there was no additional expenditure (for example, personnel time and amortization of vehicles and equipment).

2. In the case of Indonesia (Aceh), as well as Indonesia (Pidie), only the cost per death averted was given in the source cited. The World Bank authors have calculated the cost per case averted from this information using the WHO estimate of 85 percent case fatality for NNT.

3. All dollar amounts in parentheses in this section are 1989 U.S. dollars.

4. The authors would like to thank Dean Jamison for his assistance with the calculations in this paragraph.

5. The authors would like to thank Dean Jamison for his assistance with the calculations in this paragraph.

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